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CONGENITAL DEFECTS OF FEMUR, FIBULA AND TIBIA

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The question of congenital deformities and defects of the extremities is attractive because of the richness of different morphologic manifestations; it is difficult when it comes to the systematic grouping of observations, and it is extremely embarrassing when etiology is concerned. It seems that with all the scientific armamentarium of modern physicians, they are approaching the problem merely from another side and have not yet succeeded much more in detecting the underlying cause than had the observers of many hundred years ago, who interpreted the various monsters as lusus naturae. Nature, or a great vital force, in incalculable mood, enjoys and diverts itself by producing the most abstruse forms. The more modern conceptions are more mechanistic, and the thin amniotic membrane especially has frequently been accused of being responsible for the development of congenital deformities, either by inflammatory adhesions or simply by decreased amount of amniotic fluid. No doubt for a number of cases such an explanation is adequate and satisfactory, but in most instances it seems rather that endogenous factors are at work. Simple morphologic study has failed to throw light on the inner mechanism of development of congenital deformities, and new attempts will have to be undertaken by experimental biologists. The field is still entirely open.

I report here a number of instances of congenital deformities of the lower extremity, mainly affecting the femur and the fibula. I have tried to arrange the cases so that it becomes evident that congenital defects, of the femur or the fibula, for instance, as a rule cannot be classified individually, but that they are most commonly associated with other deformities. It will be easy to show that most of the patients with congenital defects of the femur have other deformities of the same extremity, and it is rather doubtful whether it is advisable to make the discrimination simply from the largest bone affected. If one reviews a greater amount of material, one gains the certain impression that there are fluent passages from hypoplastic development of the extremity,

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which can be considered as isolated, proportionate dwarfism of the limb, to true deformity due to defects in the skeleton. This fact alone points toward an intrinsic disturbance of growth of the extremity and not toward external factors, such as amniotic constriction or adhesions.

CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH PRESERVATION OF PROPORTIONS: THREE CASES

CASE 1.—The patient was a 3 year old girl. Shortness of the left leg was noted at birth. Development was normal. No other deformities occurred in the

Fig. 1 (case 1).—Congenital shortening of the lower extremity, with hypoplasia of the fibula (upper epiphysis not yet developed). The anteroposterior roentgenogram of the left foot shows marked hypoplasia of the fourth metatarsal bone.

family. Moderate valgus of the left knee was present, with external rotation of the tibia. Roentgenograms showed congenital shortness of the entire left lower extremity without more marked deformity. All the bones were evenly hypoplastic with the exception of the fibula, which was relatively shorter than the tibia and of which the upper epiphysis was not yet developed. The fourth metatarsal bone was less than half its normal size, and the toe was retracted.

CASE 2.—The patient was a 10 month old boy with a family history of shortness of the right foot in the paternal grandfather and an aunt. No gross deformity was present. There were congenital shortness of the right lower extremity and syndactylism of the second and third toes of the right foot, with moderate varus of the knee. Roentgenograms showed hypoplasia of the limb, involving all bones equally.

CASE 3.—The patient was a 1 year old boy who had been born with a short right leg. He had only three toes on the right foot. No other deformities had occurred in the family. The shortness at gross inspection seemed to involve the thigh and the leg equally; on measurement, however, the latter was shown to be

Fig. 2 (case 2).—Proportionate shortening of the right lower extremity.

more affected. Roentgenograms showed hypoplasia of the right lower extremity with a total absence of the fibula; only two inner metatarsal bones and three toes were developed.

These three cases form one group, having in common the hypoplastic development of one extremity. However, there were different degrees of involvement, which besides causing uniform retardation of growth led to suppression of certain portions of the distal part of the limb. The mildest form seems to be the lack of differentiation of the toes, resulting in syndactylism (case 2), brachydactyly (case 1) due to

maldevelopment of the metatarsal bone or hypodactyly due to absence of the lateral toes and the fibula (case 3). The proportion between the thigh and the leg is maintained, although it seems that with the suppression of certain parts of the skeleton the harmonic development of the entire extremity becomes disturbed and the part most affected does not keep pace with the less involved portion. It is thus possible that the proportion between the thigh and the leg, which in the first years of life may be normal, may gradually become changed as the function

Fig. 3 (case 3).—Shortening of the right lower extremity, with total absence of the fibula. Only two metatarsal bones have developed.

of the extremity is interfered with by the skeletal defect. There can, however, be no doubt that the instances of congenital shortening have to form the point of starting. They are most likely to direct attention toward a disturbance of growth of the extremity by intrinsic factors. However, as so little is known about the factors underlying normal growth, the question is even more difficult if pathologic growth occurs. It may give a slightly better understanding to consider congenital shortening of one extremity as a partial proportionate dwarfism of the body.

Disturbance of the function of the endocrine glands is entirely out of the question. It is a "nanosomia primordialis," based most likely entirely on constitutional factors. One has to figure on an inherited delicate mechanism which controls and maintains the relationship of the different portions of the body. (The term vis vitalis has been brought into disrepute by the mechanists, but there still seems to be just that kind of controlling factor.) Cases of hemigigantism and especially of its crossed form bear out the theory that the growth of the extremities is dominated by unknown agents which most certainly cannot be external and mechanical. Heredity is without doubt of greatest importance, and although it is true that for the congenital

Fig. 4 (case 5).—Maldevelopment of the right femur, with marked coxa vara and shortening.

defects of the lower extremity (femur and fibula) the number of instances of hereditary occurrence is very small, it is sufficient to give heredity preference as an etiologic factor. Among the three patients with congenital shortness there was one (case 3) whose paternal grandfather and an aunt showed also congenital shortness of the right foot without the absence of any part.

I consider now another group of cases in which the congenital shortening of the lower extremity was disproportionate, owing to more shortening either of the thigh or of the leg. They, of course, represent more marked degrees of disturbance of growth frequently com-

bined with extensive defects in the skeleton of the extremity. I start with the defects of the femur.

CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH LACK OF PROPORTION: DEFECTS OF GROWTH OF THE FEMUR

EIGHT CASES

CASE 4.—In a 7 year old girl the left femur was markedly shorter than the right but was not deformed. The knee joint was well developed; the tibia and the fibula were normal. The roentgenograms were discarded.

Fig. 5 (case 6).—Congenital shortening of the right femur, with coxa vara. Anterior subluxation of the knee joint.

CASE 5.—The patient was a 15 month old boy, with 4 inches (10 cm.) of shortening of the right lower extremity, all in the femur. The right knee joint subluxated anteriorly with ease when the child kicked and went back into place with a snapping noise. One sister had bilateral dislocation of the hip. Roentgenograms showed malformation of the femur, with a high degree of coxa vara.

CASE 6.—The patient was a 15 year old girl with 8 inches (20 cm.) of shortening, most of it in the femur. Marked genu valgum was present, with habitual subluxation of the tibia in an anteroposterior direction. Pes equinovalgus was present. One cousin had a dislocated hip. Roentgenograms showed hypoplasia of the femur, with coxa vara of about 70 degrees. The greater trochanter formed

Fig. 6 (case 7).—Congenital shortening of the femur, with coxa vara. Micropatella with genu valgum. Absence of the upper epiphysis of the fibula.

a marked bony prominence and almost touched the ilium. The knee joint was deformed, with a micropatella, anterior subluxation of the tibia and valgus of 35 degrees. The fibula was well developed in the upper end.

Case 7.—The patient was a 29 year old woman with 7 inches (17.5 cm.) of shortening of the left lower extremity, all in the femur. There was marked knock knee, with the foot in 30 degrees equinus deformity. She walked fairly well with a shoe extension. Roentgenograms showed marked shortening of the femur, with coxa vara of about 100 degrees. The shaft of the femur was straight; the knee joint was deformed; the lateral condyles of the femur and the patella were hypoplastic. The upper epiphysis of the fibula was absent. No pictures of the foot were available.

Case 8.—The patient was a 6 week old girl with absence of the femur. No other deformities had occurred in the family. Roentgenograms showed complete absence of the femur; the leg bones were of normal length; the upper epiphysis of the tibia was not yet developed; the acetabulum was well shaped. The patient

Fig. 7 (case 8).—Extensive defect of the right femur. Only a portion of the lower epiphysis has developed, and it is synostosed with the upper epiphysis of the tibia.

received an extension brace and was seen again two years later. Roentgenograms at that time showed that a small bony process which corresponded to an underdeveloped lower epiphysis of the femur extended from the upper epiphysis to the tibia. There was no differentiation of the knee joint, and the acetabulum and leg bones were slightly hypoplastic.

Case 9.—A 5 year old boy had multiple congenital deformities of the upper and lower extremities. Ectromelia of the upper extremities was present, with absence of the bones of the forearm. He had a lobster claw hand with the thumb and little finger present and the third and fourth fingers fused into one giant finger. He walked unaided despite maldevelopment of both thighs and congenital clubfoot on the left. Umbilical hernia was present. No other deformities had occurred in the family. Roentgenograms showed congenital defects of the femur and the fibula on the right; the upper epiphysis of the tibia formed one piece of bone with a rudimentary lower epiphysis of the femur. There was no differentiation of the

knee joint. On the left, the upper epiphysis of the tibia was separated from the lower epiphysis of the femur, indicating that the knee joint was present, but the lower epiphysis of the femur formed only a spherical bony shadow. The pelvis showed complete absence of acetabular cavities. The tibias were well developed. There was marked equinovarus deformity of the left foot, only four metatarsal bones being present.

Case 10.—A 13 month old girl had been born at full term by breech presentation. Both upper extremities were stumps without elbows or forearms. The left lower extremity was normal; the right lower extremity was much shortened and externally rotated. Roentgenograms showed an absence of the upper half of the right femur. The pointed end of the diaphysis stuck into the acetabulum, which was shallower than that on the left side. The lower epiphysis of the right femur was fused with the upper epiphysis of the tibia, and there was lack of differentiation of the cavity of the knee joint. No patellar shadow was visible (the bony nucleus was not developed on the left side either). There was shortening of the leg, with equinus position of the foot. Anterior bowing of the tibia in the lower

Fig. 8 (case 9).— *A*, congenital deformities of upper and lower extremities. *B*, defects of the femur, with lack of differentiation of the right knee joint. The acetabulums have not developed. The fibulas are absent.

portion of the middle third was present, with complete absence of the fibula. Treatment consisted of the wearing of an extension leg brace with a pelvic girdle.

Case 11.—The patient was a 14 year old boy, who had been born with a short lower right extremity. The leg and the foot were almost of the same size as those on the left. The muscles of the thigh functioned well. He walked with a prosthesis to compensate for the shortening of 13 inches (33 cm.). Roentgenograms revealed that the right half of the pelvis was considerably underdeveloped; the femur was present only in its upper and lower ends. The upper end was formed by the head and trochanter, which constituted a solid bony mass in varus position; the lower end showed both condyles fairly well shaped, with a good knee joint. The diaphysis was missing. The upper and lower ends were close together but were not in bony union. There was no patella.

The eight cases of this group represent instances of deformity of the lower extremity with the main involvement in the femur. Despite the

small number of cases one can easily recognize certain types of deformity. Case 4 has to be classified as one of real hypoplasia of the femur; that is, the bone was well shaped but diminished in all its dimensions. Here again, one may speak of a partial localized dwarfism of the skeleton. The term hypoplasia of the femur was used by Drehmann and Reiner for a certain form of congenital defect of the femur in which there is a defect or shortness of the diaphysis, whereas

Fig. 9 (case 10).—Congenital defect of the right femur, with absence of the upper half. Synostosis of the lower epiphysis of the femur with the upper epiphysis of the tibia and absence of the patella and fibula are shown.

the upper and lower epiphyses are normally developed. The deformity in case 11 would fall into this group. However, I prefer to use the term hypoplasia congenita femoris only for those conditions in which there is harmonic underdevelopment of the femur without any other defects. Nilsonne expressed doubt as to whether general hypoplasia of the femur should be classified with the congenital defects. I do not share his doubts. He was right in that hypoplasia is not a real defect,

but I conclude from my observations—frequent occurrence of hypoplasia of one bone associated with defects of others—that hypoplasia represents the mildest form of disturbance of growth, which if more marked leads to defects and even to aplasias. Most of the authors who write on congenital defects of the femur consider congenital coxa vara as the mildest form (Drehmann,[1] Reiner,[2] Nilsonne[3]). To a certain extent I agree with this view, but I believe that such a statement has to be accepted with some reservations. There is no doubt that in a number of instances coxa vara represents only a certain form of congenital maldevelopment of the femur, as in cases 5, 6 and 7. In these cases there can be no doubt about the congenital nature of the deformity. The marked shortening of the femur was noted either at the time of

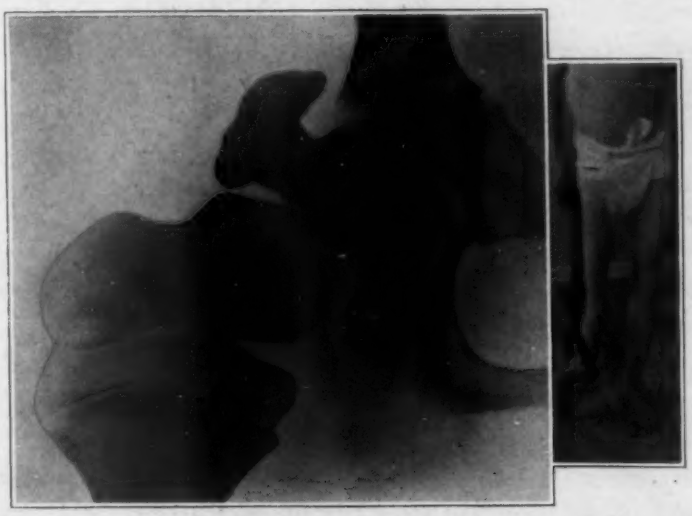

Fig. 10 (case 11).—Congenital defect of the right femur, with absence of the diaphysis and the patella, and a good hip and knee joint.

birth or shortly afterward, but certainly before the child started to walk. However, I should hesitate to accept the deformity in all the cases which come under the heading of congenital coxa vara as intimately related to the congenital defects of the femur. Only deformity which has been recognized clearly before the child started to walk should be classified as congenital coxa vara. Cases of such deformity

1. Drehmann, G.: Ueber angeborene Femurdefekte, Ztschr. f. orthop. Chir. **11**:220, 1903.

2. Reiner, M.: Ueber den kongenitalen Femurdefekt, Ztschr. f. orthop. Chir. **9**:544, 1901.

3. Nilsonne, H.: Ueber den kongenitalen Femurdefekt, Arch. f. Orthop. **26**:138, 1928.

are rare, and there is considerable shortening of the femur. In all the other cases—by far the majority—the condition probably has nothing to do with congenital defect of the femur; it most likely represents some postnatal disturbance of growth in the region of the neck of the femur which, despite many investigations, has not yet been clearly defined.

Drehmann was the first to point out the relation between congenital coxa vara and a certain form of defect of the femur which he called "apparent" defect of the femur. He noted complete absence of the upper end of the femur in a 5 year old boy. At a later examination it was noted that the bony nucleus in the head of the femur had developed, and at the age of 9 years the upper end of the shaft had united with the proximal end of the femur with the formation of a pronounced coxa vara.

It is doubtful whether in cases 5, 6 and 7 the condition was of the same order. There were marked degrees of coxa vara, especially in cases 5 and 6, but the shaft of the femur was straight. In Drehmann's cases of "apparent" defect of the femur the deformity lay mainly in the trochanteric region, and on clinical examination the most prominent portion of the femur was not the greater trochanter but the deformed subtrochanteric region. In my cases it is not unlikely that the deformity was due to a muscle imbalance at the upper end of the femur and around the hip joint. As I shall point out later, one must assume that, owing to influences similar to those from which the skeletal part had suffered in its development, the musculature also was far from being perfectly normal. Besides phylogenetic hereditary factors, it is especially muscle action and weight-bearing which influence and cast the shape of the bone. In cases of congenital deformity of the lower extremity the importance of the musculature has been neglected. Still, it is well known that a disturbance in the equilibrium of the muscles around the hip joint will alter the configuration of the neck of the femur (coxa valga after infantile paralysis or progressive muscular dystrophy); so it may be that a maldeveloped musculature of the femur is responsible for the frequently noted coxa vara in cases of congenital deformity, if the disturbance of ossification alone is not sufficient to explain the deformity.

Cases 8, 9 and 10 are instances of the more common forms of congenital defect of the femur. In most of the cases reported in the literature the upper half of the femur was involved. In my three patients, examined in early childhood, the upper end of the femur was entirely absent (possibly at a later examination the upper end of the femur also became ossified, although there have been autopsies on adults which showed the upper portion of the femur to consist only of a dense strand

of fibrous tissue which connected the acetabular cavity with the upper end of the defective femur). In all three cases (one of bilateral deformity) the lower end of the femur was only of rudimentary development, and in all three the knee joint was not differentiated. The lower part of the femur was synostosed with the upper epiphysis of the tibia. The lower epiphysis of the femur did not resemble the normal shape of the condyles; it was, as a rule, only a small exostosis-like bony prominence. If a part of the diaphysis had already developed, it ended typically pointed (like concentrically atrophic bony fragments) in the soft tissues. In cases of more marked deformity the knee joint may be almost at the level of the hip. In such cases the thigh forms a cone-shaped mass of flesh with fairly good muscle action.

Of interest is case 9, in which the first roentgenogram revealed complete absence of the femur. Two years later a rudimentary lower epiphysis could be observed. From the literature it seems that complete absence of the femur is an extremely rare condition and should not be diagnosed before the tenth year of life, as the diagnosis in early childhood is likely to be erroneous (Reiner [2] and Drehmann [1] did not even include it in their classification). The same seems to be true of absence of the fibula. The ossification in these cases is retarded, and the roentgenogram may change considerably at greater intervals.

A rare condition occurred in case 11. The upper and lower ends of the femur were well developed, the patella was absent and the leg was of the same size as that on the normal side. As a rule, the defect of the femur involves the upper end of the bone; in this case almost a pure defect of the diaphysis was present. There are apparently only two reports of deformity of this kind in the literature: The skeleton of an adult was described by Vrolik [4] and a case in a young child was described by Adrian.[5] In our patient, a 14 year old boy, the condition cannot be considered simply as absence of the diaphysis. The fact that the trochanter and the head of femur were united by a rudimentary neck discloses that at least a small portion of the diaphysis had developed. The condition, however, came close to complete absence of the diaphysis without truly being so.

From my relatively small amount of material it can already be seen that congenital defect of the femur is frequently associated with other deformities of the skeleton, especially of the same extremity, but it is not always true that the more pronounced the defect of the femur the more likely it is that other deformities are present. From the cases in the literature I should say that in about two thirds of the cases

4. Vrolik, quoted by Adrian.[5]

5. Adrian: Ueber kongenitale Humerus- und Femurdefekte, Beitr. z. klin. Chir. **30**:401, 1901.

complicating deformities are present. Absence of the patella and absence of the fibula are the most frequently observed complicating deformities. In two of my cases (9 and 10) there was also ectromelia of the upper extremities; in case 9 clubfoot was present on one side; in case 10 there were anterior bowing and shortening of the tibia. In three cases, besides the hypoplasia of the patella, the entire knee joint showed maldevelopment with a valgus deformity and a snapping habitual anterior subluxation of the tibia.

It is of interest that none of my patients with true defect of the femur had evidence in the history that the condition was hereditary, and to my knowledge in none of the cases reported in the literature did the history show other members of the family to be affected by congenital deformities. This is certainly surprising, as milder deformities, such as congenital shortening or even coxa vara congenita, show hereditary or familial occurrence. Still, I believe that in most of the cases the condition is caused by endogenous factors. However, external influences have to be considered in some cases of congenital deformity of the femur, as is shown by the following case:

CASE 12.—The patient was a 3 month old girl, one of twins born at full term by normal delivery. She was born with deformed femurs and with flexion contracture of the left knee. She had umbilical hernia. The twin sister was said to have shown a similar condition; she had a fracture of one femur and died at the age of 3 months. Roentgenograms of the patient showed a marked varus kink in the middle third of the right femur, suggestive of an intra-uterine fracture. The left femur showed similar but less marked bowing at the junction of the upper and the middle third.

It is rather doubtful whether the condition in this case can be classified with the group of congenital defects of the femur. Two cases have been reported in the literature (Lotheissen [6] and Kindl [7]) in which the congenital defect was present in a twin. The same deformity of both femurs, especially of the right, suggests rather an external bending factor due to the crowded uterine cavity. I do not believe that the deformity was due to an intra-uterine fracture in the sense of a traumatic dissolution of the continuity of the bones. This is an extremely doubtful occurrence. It was more likely caused by a continuous bending stress on the soft embryonal bone, due to the abnormal position of the embryo in utero. This case differs from the other cases of congenital deformity of the femur in that one must consider a continuous modeling trauma as the causative factor of the deformity, which means that the deformity did not develop at one time, as in a fracture, but gradually. Such trauma has been accused in the cases of Reiner and

6. Lotheissen, quoted by Nilsonne.[3]

7. Kindl, quoted by Nilsonne.[3]

Drehmann in the sense that a tight amnion by pull and pressure leads to occlusion of the vessels and impairment of the blood supply to the femur. Reiner, especially, worked out a theory, based on the different vessel systems in the growing femur, to explain the different forms of congenital defect of the femur, but despite the great effort he put into his task, the idea nowadays seems obsolete and far fetched. How-

Fig. 11 (case 12).—Congenital deformity of both femurs, probably due to chronic bending stress in utero.

ever, it cannot be denied that especially for the defects in the subtrochanteric region Reiner's theory of occlusion of the vessels is well founded; he already had recognized this part of the femur as a locus minoris resistentiae. In most instances, however, one must consider endogenous factors leading to the disturbance of growth long before ossification begins. Everything points toward an early origin of the

lesion, so that a vitium primae formationis seems to be most likely. Disturbance of vascularization by occlusion of the vessels may be a helpful supposition in some cases, but it can by no means give a full understanding of all the various forms of congenital deformity of the femur. The same is true of intra-uterine trauma, which, even in the mitigated form outlined, can be accepted as an etiologic factor in only a few cases.

CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH LACK OF PROPORTION

Defects of Growth of Fibula (Seven Cases).—I now have to consider a group of cases of disproportionate congenital shortness of the lower

Fig. 12 (case 13).—Anteroposterior and lateral views of the right lower extremity, with complete absence of the fibula and anterior bowing of the tibia. Only three toes are present.

extremity, with the main involvement in the bones of the leg. I divide the material into two groups: (*a*) defects of the fibula and (*b*) defects of the tibia. As the defects of the femur are often associated with maldevelopment of the other bones of the leg, it is easy to show that the same is true for the defects of the other leg bones which often appear with a congenital maldevelopment of the femur. For this reason it is unsatisfactory to classify the congenital lesions of the lower extremity as defects of the femur and as defects of the fibula or the tibia. I do this only because it is an easier way to present the material.

CASE 13.—The patient was a 10 month old boy, born with a deformed right foot and leg. No other congenital deformities had occurred in the family. Roentgenograms showed complete absence of the fibula, with shortening of the tibia and marked anterior and inward bowing in the middle third. There was reenforcement of the cortex at the concavity. The foot was in a marked equinovalgus position; two lateral toes were missing. The total shortening was 2½ inches (6.2 cm.). An operation was performed, consisting in lengthening of the achilles tendon, posterior capsulotomy and oblique osteotomy through the tibia at the site

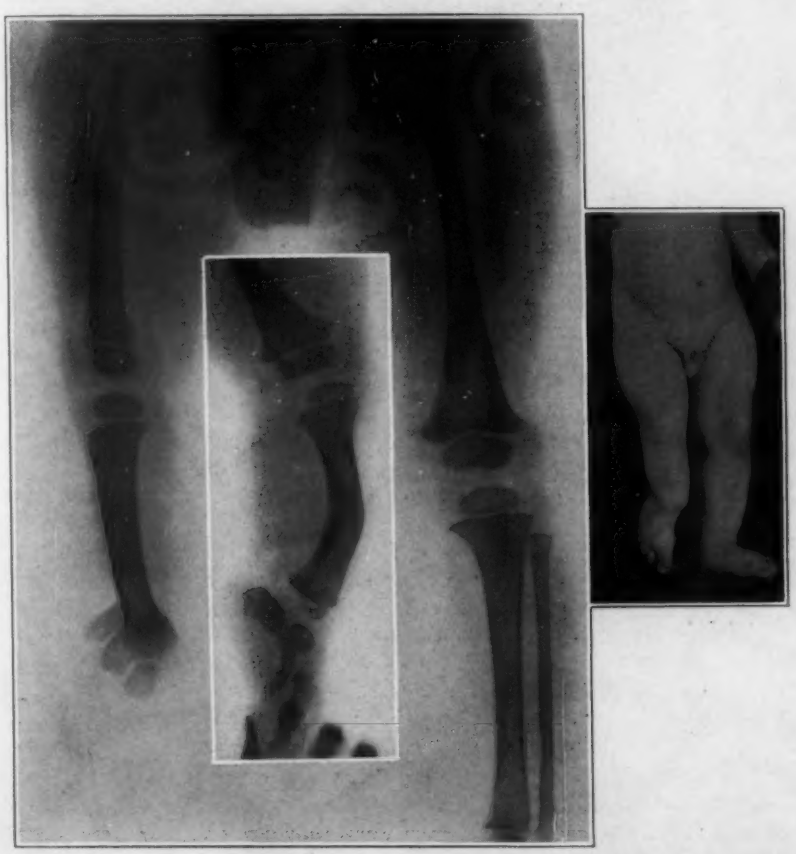

Fig. 13 (case 14).—Disproportionate shortening of the right lower extremity, with complete absence of the fibula and bowing of the tibia.

of deformity. Not much correction was obtained. A peculiar finding was that there was practically no achilles tendon; the muscle fibers extended down to the os calcis. The prosthesis with which the patient walked was satisfactory. Amputation at a later date was considered.

CASE 14.—The patient was a 17 month old boy with about 2 inches (5 cm.) of shortening of the right lower extremity, with anterior bowing of the tibia, marked equinovalgus of the foot and metatarsus varus. When he put his weight on the right foot, he stood on the inner malleolus. Roentgenograms showed complete

absence of the fibula, with shortening and thickening of the right tibia. There was anterior bending in the middle third, with reenforcement of the posterior cortex. The right femur was also considerably shorter than the left, with varus and forward bending at the junction of the upper and the middle third. The bones of the foot were well developed. A wedge osteotomy was performed through the tibia, with correction of the metatarsus varus and lengthening of the achilles tendon. Two years later the shortening amounted to 4 inches (10 cm.), 2 inches (5 cm.) in the femur and 2 inches in the lower part of the leg. An extension brace was applied, and amputation at a later date was considered.

Case 15.—The patient was a 6 week old boy, born with a short left lower extremity and syndactylism of the fingers. Roentgenograms showed marked shortening of the extremity, with complete absence of the fibula, and only four toes present in the foot. There were considerable anterior bowing of the tibia in the middle third, equinus position of the foot and absence of the astragalus. Multiple deformities were present in the fingers, with hyperphalangism and syndactylism.

Case 16.—The patient was a 22 year old man, born with a short right lower extremity and clubfoot. Casts were applied in early infancy, and some operations were performed. No treatment had been given since he was 2 years of age. The deformity of the foot was never corrected, and at the age of 8 years it went into a rigid equinus position. He had worn an extension appliance with a false foot. He had pain in the foot and desired amputation.

The total shortening was 6¾ inches (16.8 cm.), 2¾ inches (6.8 cm.) in the femur and 4 inches (10 cm.) in the lower part of the leg. There was good motion in the knee joint but little motion in the ankle joint. The achilles tendon was very tight; the plantar fascia was contracted. Most of the deformity lay in the forepart of the foot. Roentgenograms showed marked shortening of the tibia, which was relatively thick. The lower end was deformed; the joint surface, instead of being horizontal, was in a plane inclined inward, forward and downward. The fibula was present in a hypoplastic stage; it was situated along the lower third of the tibia but did not form the outer malleolus. It still showed division into two epiphyses and one diaphysis. The epiphyseal plates, however, had already disappeared. The foot was markedly deformed; it was kept in extreme equinovalgus position, with adduction of the forepart of the foot and marked cavus. The astragalus had slipped forward; the os calcis showed synostosis with the cuboid bone. The scaphoid bone was wedge-shaped owing to the cavus deformity and was slightly displaced dorsally. The toes and metatarsals were well developed.

Case 17.—A 4 year old boy had been born with clubfoot. He was treated with casts, and the achilles tendon was lengthened twice. Deformity recurred; especially marked metatarsus varus was present. Roentgenograms showed marked hypoplasia of the fibula, which, however, despite its shortness, resembled closely in shape the normal fibula. There were upper and lower epiphyses, but the lower one did not form the outer malleolus. There was valgus of the heel combined with marked metatarsus varus. The whole right foot was smaller than the left. The bony nucleus of the scaphoid had not yet developed (it was present on the left side). There were only four metatarsal bones; the fourth was thicker than the others and was a combination of two. Webbing of the fourth and fifth toes was present.

Case 18.—The patient was a 9 year old boy, who had been born with a lobster foot and anterior bowing of the tibia. There was 3½ inches (8.7 cm.) of shorten-

ing, almost all below the knee. Roentgenograms showed a pronounced deformity of the tibia. It was short, thick and clumsy. The lower epiphyseal plate was very irregular, and the lower epiphysis was small and was represented only by the inner malleolus. The fibula was short and thin and displaced backward and consisted only of a lower epiphysis and a diaphysis. There was no malleolar mortice. The foot was placed laterally to the lower end of both leg bones, which produced a marked valgus kink. It was a typical lobster foot. It seemed that the astragalus

Fig. 14 (case 15).—Congenital shortening of the right lower extremity with complete absence of the fibula and the astragalus.

and the os calcis had fused into a big heel bone. The first and the fifth toe were well developed; there was a rudimentary third toe in the form of a small metatarsus which was in partial bony union with one cuneiform bone. There were another well developed cuneiform bone for the first toe, a cuboid bone and a misshapen scaphoid bone. The other bones of the foot were not developed. The foot was extremely flat.

Amputation at the lower third was performed. The specimen was carefully dissected. Because of the rareness of the deformity, I give here a more detailed description. The foot was very short and lacked completely a longitudinal arch. It was a typical lobster foot, with two outer toes and a rudimentary third toe which had only a small metatarsal bone pointing toward the skin of the dorsum. The inner malleolus formed a large bony prominence at the inner side and reached down to the plantar surface. The inner and outer malleoli were in different frontal planes, at a distance of about 1 inch (2.5 cm.) from each other.

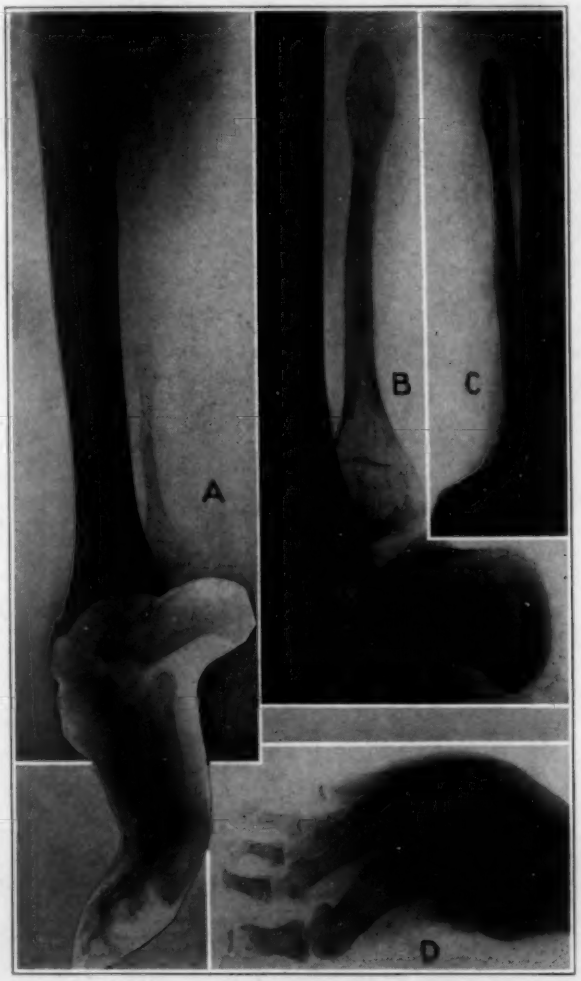

Fig. 15 (case 16).—Congenital hypoplasia of the fibula, with marked cavus deformity of the foot and metatarsus varus. *B* and *C* are lateral and anteroposterior views of the fibula, still showing both epiphyses and the diaphysis.

After removal of the skin a well developed superficial fascia was noted. The muscle groups were all present and were separated from each other by fascial spaces. The gastrocnemius muscle formed a short achilles tendon which was

inserted in the tuber ossis calcis. Both peroneus muscles were present; they left the shaft of the fibula at its lower third and ran to the outer border of the foot. Both were inserted into the tuberosity of the fifth metatarsal bone after passing the dorsal side of the calcaneocuboid joint. The space between the lower third of the fibula and the peroneal tendons was filled with an accessory muscle which formed a muscular bridge between the lower end of the fibula and the os calcis. The extensor group took its origin from the fibula and the intramuscular septum; it formed a muscular leaf of considerable strength, almost in the sagittal plane. Over the dorsum of the ankle the muscle leaf divided into several tendons; one,

Fig. 16 (case 17).—Congenital hypoplasia of the fibula with valgus of the heel and metatarsus varus. Syndactylism of two lateral toes.

inserted at the inner side of the foot, has to be considered as the tibialis anticus. Two tendons went to the first toe; one ended at the metatarsophalangeal joint and the other at the base of the second phalanx. One rather strong tendon was inserted at the base of the rudimentary toe, covered in part by an atrophic extensor digitorum brevis. The most lateral part of the extensor group formed a strong tendon which went to the base of the fifth toe and then ran along its dorsal side to the base of the second phalanx. None of the muscles seemed to have had real action. The flexor group showed good differentiation of the tibialis posterior, flexor hallucis brevis and flexor muscles of the toes. The posterior tibial vessels

and nerve were present; the nerve was considerably flattened where it came to the inner side of the foot. The tibialis posterior muscle ran behind the inner malleolus; its tendon was flat and was inserted on the plantar side of the scaphoid bone. The flexor digitorum communis muscle passed, together with the posterior tibial nerve and vessels, above the abductor muscle of the first toe to the plantar

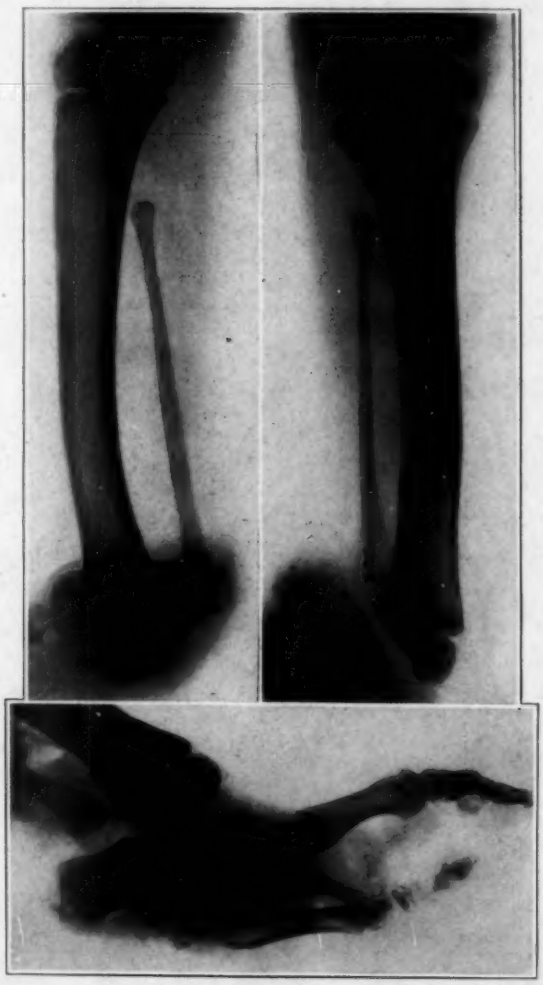

Fig. 17 (case 18).—Anteroposterior and lateral views of the right leg and foot, showing congenital hypoplasia of the fibula with shortening of the tibia, absence of the astragalus, marked ankle valgus and lobster foot.

side of the foot. Here the tendon divided into two parts, which passed through the tendon sheaths to the first and fifth toes. The short plantar muscles were well developed. The quadratus plantae, lumbricales and practically all the thenar and hypothenar muscles were present.

The dissection of the joint between the tibia, the fibula and the heel bone revealed a strong ligament running from the anteromedial side of the lower end of the tibia to the inner cuneiform bone, reenforcing the articulation. The capsule was thick and tight; it was cut along its entire anterior inferior insertion. Two joint surfaces were present on the medial side of the os calcis for the articulation with the lower end of the fibula and the tibia. They were separated from each other by a capsular septum which came down from the border between the outer malleolus and the lower end of the tibia. The larger joint surface, which extended also on the inner side of the os calcis, was for the tibia. This joint surface was covered by smooth hyaline cartilage, which at the joint margins gradually blended into the thick fibrous tissue of the joint capsule. The inner malleolus had no

Fig. 18 (case 18).—Lobster foot. A detailed description appears in the text.

articulation with the os calcis. The joint with the fibula was smaller and was also covered by hyaline cartilage. The articulation was constructed so that both leg bones, the tibia in an anteromedial position and the fibula in a posterolateral position, articulated with the inner side of the os calcis, which was inclined to the longitudinal axis of the leg. The joint surfaces lay, therefore, in a plane which extended from in front and above and lateral to downward, backward and inward.

Case 19.—The patient was a 3½ year old boy, born with deformities on both lower extremities. No other deformities had occurred in the family.

On physical examination marked shortness of the left lower extremity was noted, with valgus deformity of the knee and marked calcaneovalgus of the foot. There was an anterior and inward kink at the junction of the middle and the lower third of the tibia. Directly over the prominent portion of the tibia a small shallow

dimple could be seen in the skin, not adherent to the bone and with normal superficial cutaneous structure. There was no evidence of scar formation. The fibula could not be palpated. The foot showed a marked deformity: Only the first toe was present and fully developed in all its parts. All the other toes were missing. There was only a small tag of skin close to the short outer border of the foot. The os calcis could be palpated; it was in marked equinovalgus position. The skin over its anterior edge showed a thick callus. The achilles tendon was tight. The inner malleolus was prominent, and the foot was flat.

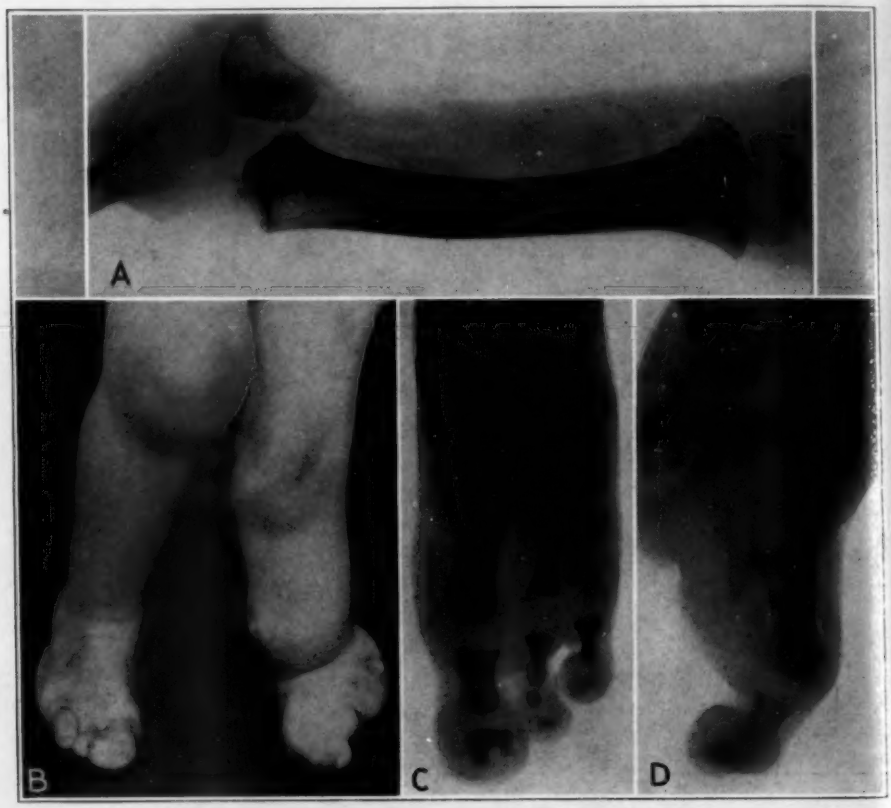

Fig. 19 (case 19).—*A*, complete absence of the fibula, with shortening and bowing of the tibia. *B*, malformation of the feet and marked valgus of the left foot, with shortening of the left lower extremity and genu valgum. *C*, anteroposterior view of the right foot. *D*, anteroposterior view of the left foot.

The right lower extremity was well developed, with the exception of the foot. The lower end of the fibula was displaced backward, with anterior displacement of both peroneal tendons. The foot was narrow and showed only three toes. There was syndactylism of the first and second toes, the latter being hypoplastic. The heel was in slight valgus; the foot was flat. The skin over both lower extremities was free from amniotic scars. There was 2 inches (5 cm.) of shortening of the left leg.

Roentgenograms showed complete absence of the fibula on the left, with marked shortening and some anterior and inward bowing of the tibia, the lower epiphysis of which was very small. There were only two tarsal bones, one of which was the os calcis and the other probably the cuboid bone. The first toe was present, with the metatarsal bone and two phalanges. No other bones were developed. On the right side the tibia and fibula were well developed. The foot showed an astragalus and a deformed os calcis. Three toes were present; the endphalanx of the big toe showed a skeletal syndactylism. The patient was fitted with an extension prosthesis with a pelvic girdle and a free knee. Amputation of the leg at a later date was advised.

Case 20.—The patient was a 13½ year old girl, born with a short right leg and valgus deformity of the foot. She had been treated in the clinic since the

Fig. 20 (case 20).—Congenital hypoplasia of the fibula with shortening of the right leg. *A*, slight genu valgum and marked valgus of the ankle. *B*, lateral view of the ankle region showing irregular calcification of the diaphysis; synostosis between the astragalus and the os calcis. *C* and *D*, anteroposterior and lateral views of the fibula, showing both epiphyses and the diaphysis. *E*, longitudinal section through the specimen, showing the cartilaginous epiphyseal lines, with irregular cartilaginous islands in the diaphysis.

age of 5 weeks by manipulation of the foot and a leather shell. Roentgenograms taken at the age of 2 years showed absence of the fibula. When 1 year old she had a plastic lengthening of the achilles tendon which, at the age of 4 years, had to be repeated, with a posterior capsulotomy. The foot, after that, still showed a tendency to turn to a valgus position, which, however, could be well overcome by an Orr brace. When she was 5 years old, a plastic lengthening of the peroneal tendons was performed. At that time the roentgenograms showed small bony frag-

ments at the lower third of the tibia. They were exposed at the time of operation, and from the lower tip a tendinous band the size of a little finger was noted running down to the os calcis. The lengthening of the peroneal tendons gave little correction; cutting the tendinous band improved the condition moderately. The achilles tendon was also lengthened (for the third time) and a brace was applied. When the patient was 11 years old, the leg was 2 inches (5 cm.) shorter, and there was marked valgus deformity of the heel. The foot was flat, and very little motion was present in the ankle joint. Operative correction of the valgus of the ankle was attempted. No subastragaloid joints were noted; the astragalus was synostosed with the os calcis. The joint surfaces of the tibio-astragaloid joint were almost horizontal instead of convex, thus allowing only a small amount of gliding motion. The Chopart joint line was fused. A Gleich osteotomy was performed through the os calcis, and the fragments were held in apposition by a steel pin. A short leg brace with a valgus strap was applied. The deformity of the foot was well corrected by the operation. When the patient was 13½ years old, the right leg was 3 inches (7.5 cm.) shorter than the left. An operation for lengthening the tibia was performed, and the hypoplastic fibula was entirely removed subperiosteally. A lengthening of 6 cm. was obtained. At the time of writing the child is in a long leg cast.

Roentgenograms taken when the patient was 11 years old showed the lower end of the tibia to be fairly well developed and articulating with the astragalus, which was misshapen, flat and synostosed with the os calcis. There was no subastragaloid joint. The fibula formed a short (2½ inch [6.2 cm.]) ovoid piece of bone, which showed very irregular calcification of its middle half, which corresponded to the diaphysis. This irregular shadow was surrounded by apparently normal periosteal bone, so that one gained the impression that the calcified cartilage of the diaphysis did not undergo normal vascular resorption and that therefore the growth in length was interfered with. There was no external malleolus; the entire fibula lay in soft tissues.

At the age of 13½ there was practically the same relationship of the tibia to the foot. The fibula had increased a little in length (3 inches [7.5 cm]) and showed definitely two epiphyses and one diaphysis of coarse bony trabeculation. The irregular calcified shadow had disappeared from the diaphysis. The right tibia was well shaped but was much shorter than the left.

I give a detailed gross and microscopic description of the removed hypoplastic fibula because it was the first congenital defect of the fibula which was subjected to careful histologic examination. The fibula represented a more or less cylindric piece of bone 3 inches (7.5 cm.) long and ¾ inch (1.8 cm.) wide, with a crest on the inner side, facing the tibia. The surface showed a smooth, thin cortex, from which the periosteum had been stripped away. There were two division lines of cartilaginous appearance separating the poles from the diaphysis: epiphyseal plates. The upper epiphyseal plate seemed to be complete, the lower was incomplete, with a synostosis between the epiphysis and the diaphysis on the outer side. The whole specimen represented a hypoplastic form of fibula with three centers of ossification, but otherwise the normal shape of the fibula was not reproduced. On a longitudinal section, very coarse spongy bone could be seen, with fatty and hematopoietic bone marrow. The epiphyseal plates were of irregular shape and were frequently interrupted by bone marrow spaces. Many small islands of cartilage which could easily be traced to the epiphyseal plates were included in the diaphysis. In the midline, especially, there was a whole path marked by cartilaginous bodies connecting the most diaphyseal portions of both epiphyseal plates, which means that the epiphyseal lines were not transverse but

more or less funnel-shaped, with the apex toward the center of the diaphysis. It is clear that the cartilaginous islands included in the diaphysis could not be considered simply as fragments of the epiphyseal plates; it is better to consider them as remnants of the cartilaginous, preformed diaphysis. They did not undergo complete enchondral ossification and became included in and separated by the subsequently developing marrow spaces.

On histologic examination the epiphyseal plates were shown to be very irregular, with many degenerative changes in the hyaline cartilage. There was no marked difference between the epiphyseal and the diaphyseal side, present under normal conditions. The lack of difference was due mainly to the fact that even at the diaphyseal side there was little active enchondral ossification. In a few exceptional places the three cardinal stages of enchondral ossification could be noted on the diaphyseal side: (1) proliferation of cartilaginous cells with column formation and (2) preparatory calcification of ground substance, followed by (3) osteoclastic or vascular resorption, with formation of primary spongy bone. The rule, however, is the lack of proliferation of cartilage. There was an irregular zone of calcification present throughout, but this zone rarely became resorbed and replaced by bony tissue. As is typical of a quiescent stage of the process of enchondral ossification, the calcified surface of the epiphyseal disk was covered by a more or less coherent bony lamella. This was a normal finding on the epiphyseal side of the cartilaginous disk, where, as a rule, enchondral ossification was very little active; however, the presence of the bony lamella at the diaphyseal side in a 14 year old person is entirely pathologic. The retardation and small amount of activity of enchondral ossification was also revealed by the absence of inclusion of the calcified cartilage in the bony trabeculae. Normally, the spongy bone close to the epiphyseal plate shows such inclusion, which gradually becomes removed, with static transformation of the primary spongy bone. These inclusions are more frequent the more rapid the enchondral ossification, and vice versa, which means that the better the secondary transformation of bone can keep pace with the enchondral ossification, the quicker they will disappear. The irregular islands of cartilage, which already at gross inspection were observed to be included in the marrow spaces, consisted of mature hyaline cartilage of the same histologic appearance as the cartilage of the epiphyseal disks. Most of these islands were surrounded by a thin bony lamella, and in a few places signs of enchondral ossification were observed, but without proliferation of cartilage cells. The lack of proliferation and the presence of vascular resorption suggested that these cartilaginous islands would ultimately become resorbed completely. The bone marrow in the epiphyses and the diaphyses showed no differences. It was purely fatty, well vascularized and contained cancellous bone of mature lamellar structure. The thin cortical bone on the surface showed considerable lacunar resorption on its periosteal side. The poles of the epiphyses showed the insertion of dense fibrous tissue with the interposition of a zone of calcified fibrous bone.

Case 21.—The patient was a 14 year old boy with shortening of the right leg and marked valgus of the ankle. The patient took a prize at a baby show when he was 7 months of age. No deformity was noticeable at birth. He had limped ever since he learned to walk. The right foot turned outward; the inner malleolus formed a marked bony prominence. When he was 5 years old, roentgenograms were taken, which showed two areas of rarefaction in the diaphysis of the fibula. The lower focus was explored surgically. A complete pseudo-arthrosis of the fibula resulted between the middle and the lower third of the fibula. The leg did not develop well; the shortening increased during five years of observation and amounted at the time of admission to 1½ inches (3.7 cm.).

Roentgenograms showed the shaft of the fibula to be atrophic, with cystic areas at the junction of the upper and the middle third and of the middle and the lower third. After the exploratory operation a pseudo-arthrosis developed at the junction of the middle and the lower third, with concentric atrophy of the ends of the shaft. The entire fibula was relatively short; especially the outer malleolus was high. The tibia was well developed, with the exception of the lower epiphysis, which was small. There was a constant increase of the valgus deformity of the ankle during the various intervals of observation. I consider the condition a relatively mild disturbance of development of the fibula, with pseudo-arthrosis of the diaphysis, resulting in shortening of the leg and marked valgus of the ankle.

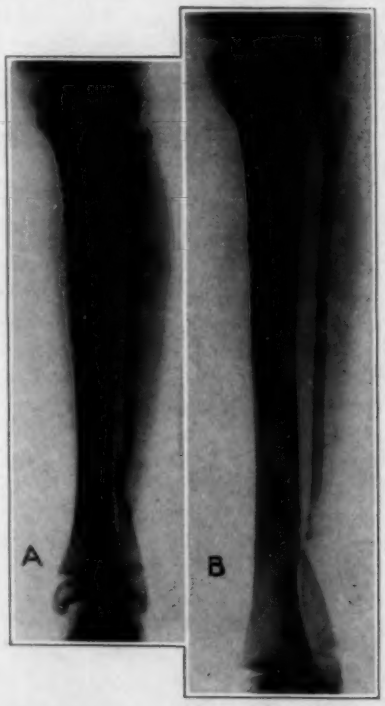

Fig. 21 (case 21).—Congenital hypoplasia of the fibula, with defects in the shaft, and valgus deformity of the ankle. *A*, fracture at the junction of the middle and the lower third (1930). *B*, pseudo-arthrosis at the site of the fracture (1935).

To correct the valgus deformity, a supramalleolar wedge osteotomy through the tibia was performed. To stabilize the foot and to prevent recurrence, a heavy bone graft was placed from the lower metaphysis of the fibula to the tibia, so as to cause harmonic growth of the tibia and fibula. To compensate for the shortening of the right leg, the lower epiphysis of the fibula and of the tibia were obliterated on the left. The operation is too recent to judge the result at the time of writing.

COMMENT

It is surprising to observe that there have been made several classifications of the congenital defects of the femur (Reiner, Drehmann,

Nilsonne) but that no attempt has been made to classify the different forms of congenital defect of the fibula, although the number of cases reported in the literature is far greater. Reports of more than two hundred cases were collected by Haudek,[8] Scharff[9] and Nutt,[10] whereas Nilsonne's careful review of the literature on congenital defects of the femur disclosed only seventy-two cases, to which he added ten of his own. All the differentiation made of the congenital defects of the fibula is that they are either total or partial, unilateral or bilateral. Still, the survey of a great number of cases in the literature and of my own eleven cases (only one of bilateral deformity) shows clearly that there are certain types which repeat themselves with great regularity. I suggest the following scheme of classification:

A. Complete Absence of the Fibula.—This, according to the literature, is by far the most frequently observed form (more than two thirds of all cases reported). This, however, has to be accepted with great care. Most of the cases reported occur in young children, who on clinical and roentgenologic examination may show total absence of the fibula but who a few years later may present a rudimentary fibula in the roentgen picture. In case 20, for instance, the condition was considered as total absence of the fibula until in the fifth year of the life of the patient an irregular bony focus appeared, which gradually developed into a hypoplastic fibula. I am certain that the same would have been true in a great number of cases reported in the literature had the patient been observed longer. Therefore, I believe that the diagnosis of absence of the fibula should not be made before at least the fifth year of life. There are, however, a sufficient number of adults with complete absence so that there cannot be doubt about the occurrence of this condition. It is certain that total absence of the fibula occurs much more frequently than total absence of the femur or the tibia. Absence of the fibula is probably more frequently observed than that of any other long tubular bone.

B. Partial Absence of the Fibula.—Considering the ages of the patients whose cases have been reported in the literature and of my own patients, and considering also the possibility of a late partial development of the fibula, I believe that the partial absence of the fibula is as frequent as the total absence, probably even more frequent. The

8. Haudek, M.: Ueber kongenitalen Defekt der Fibula und dessen Verhalten zur sogenannten intrauterinen Fraktur der Tibia, Ztschr. f. orthop. Chir. **4**:326, 1896.

9. Scharff, A.: Ueber kongenitalen Defekt der Fibula, Ztschr. f. orthop. Chir. **23**:391, 1909.

10. Nutt, J. J.: Congenital Fibular Defects, Surg., Gynec. & Obst. **37**:475, 1923.

defect may involve different portions; so subdivisions of this group are necessary.

1. Upper part present, lower absent, head of fibula palpable, outer malleolus absent. This defect is either complete absence of the diaphysis and the lower epiphysis, or the upper epiphysis is in connection with a diaphysis of varying length. This deformity seems to be relatively frequent; however, it was not present in any of my cases.

2. Lower part present, upper part absent. The outer malleolus can be palpated in place, or it is hypoplastic and does not help to form a malleolar mortice. It regularly is in connection with the diaphysis, which is thinner and shorter than normal. The upper epiphysis is completely absent. This deformity was present in two of my cases (9 and 18) and probably also in case 1.

3. Upper and lower epiphyses present, diaphysis defective. The whole bone is smaller than normal, the diaphysis is especially thin and interrupted in several places or it ends with two pointed ends near the middle, thus forming a pseudo-arthrosis. This deformity is least frequently observed (case 21).

C. Hypoplasia of Fibula.—In this condition both the epiphyses and the diaphysis are developed, but the whole bone is hypoplastic and, as a rule, is located along the lower third of the tibia without participation in the formation of the ankle joint. As a rule, these hypoplastic fibulas are considered in the literature as showing an absence of the upper half, which they do not. There are no parts absent. The constant position along the lower third of the tibia instead of in the middle, as one would expect, is most likely due to the more intense growth in length in the upper epiphyseal plate of the tibia, by which the fibula apparently gradually becomes displaced downward. This hypoplastic form is the most interesting type. It either resembles a normal fibula closely in its shape or it is only an ovoid or cylindric piece of bone which has a distinct likeness to the embryonal cartilaginous rodlike preformed fibula. I observed it in three of my cases and found it described exactly in the same form in reports of several other cases in the literature. I had occasion also to examine such a hypoplastic fibula histologically.

From the comparison of the roentgenograms taken at two different periods of development and from gross and histologic examinations I believe that I can conclude that some disturbance in the anlage of the fibula must have taken place. It is impossible to say of what kind this disorder was, but it certainly led to a retardation of growth. Ossification did not take place before the fifth year of life and then occurred in a way which showed clearly that the mainly affected part was the

diaphysis, whereas the ossification of the epiphyses was not greatly disturbed. Histologically, an explanation for the changes could be found in a pathologic process of enchondral ossification, which was abnormal in two phases: There was practically no proliferation of cartilaginous cells and very little vascular resorption. The preparatory calcification, however, was undisturbed. The roentgenograms also revealed that the diaphysis remained in a calcified cartilaginous stage for a long time. The three cardinal phases of enchondral ossification, proliferation of cartilage, preparatory calcification and vascular resorption, have to harmonize for normal growth in length. If proliferation stops but resorption proceeds, the epiphyseal disks disappear, as is the case about the seventeenth year of life. If proliferation and resorption are deficient, the epiphyseal disks may remain open for many years and even throughout life, as is the case in certain forms of true dwarfism and also in nanosomia pituitaria, due to destruction of the anterior lobe of the hypophysis. The histologic changes in my cases compare well with those noted in such cases of dwarfism. The gross appearance of the fibula and the histologic changes, therefore, lead one to believe that one deals with a partial localized dwarfism of the skeleton, affecting the fibula, as I assumed before for certain forms of congenital shortening of the extremity. It seems not only that the ossification of the diaphysis was retarded, but that there also came apparently very quickly an exhaustion of the ossifying power of the diaphysis, which therefore included many cartilaginous islands.

One abnormal structure which has played a certain rôle in the literature is the thick fibrous band which in some cases of absence of the fibula or the femur is observed in place of the bone. Haudek [8] and Krebser [11] considered these bands as proof that the defective bone had a normal anlage but that its further development, to a certain period of embryonal life, was stopped either completely or partially by an external force (amnion). This leads, then, to total or partial congenital absence. From the presence of these fibrous bands the observers concluded that the deformity cannot be a vitium primae formationis and that a mechanical force acting in early embryonal life is responsible for it. I do not think that the presence of those fibrous strands has such a decisive importance. I observed this band uniting the lower epiphysis of the dwarflike fibula with the os calcis. As both the epiphyses and the diaphysis had developed, or, in other words, the entire fibula was present although in a hypoplastic stage, the fibrous strand cannot represent the anlage of the fibula disturbed by an external force. It is simply fibrous tissue which in part may be considered as supporting

11. Krebser, E.: Kasuistische Beiträge zur Kenntnis der kongenitalen Fibuladefekte, Ztschr. f. orthop. Chir. **23**:167, 1909.

substance for the musculature, in part simply as connective tissue filling a defect. The same kind of tissue may be encountered between the ends of the bone after extensive resection of the diaphysis, resulting in pseudo-arthrosis of the type caused by defect.

Associated Deformity of Tibia.—Local dwarfism or hypoplasia of the fibula, however, is only a symptom of a more extensive disturbance of growth affecting the extremity. The defect of the fibula is frequently combined with a characteristic deformity of the tibia and of the foot. I do not intend to give here a complete clinical picture of the congenital defect of the fibula. This has been done already in a number of good articles (Haudek,[8] Scharff,[9] Gaenslen,[12] etc.), but I do want to say a few words about this deformity of the tibia.

It is typically an anterior and sometimes also an inward bowing of the diaphysis, resulting in shortening and thickening of the bone. The kink is either in the middle third or at the junction of the middle and the lower third. Frequently the skin over the apex of the curve shows a small retraction, a dimple.

The deformity of the tibia has been interpreted by many authors as due to an intra-uterine fracture; the dimple was considered as the scarred place where one of the fragments had perforated the skin. Sperling,[13] however, showed conclusively that a trauma of the strength necessary to break an embryonal bone would sooner lead to a rupture of the uterine wall and would be followed rather by abortion than by fracture. Haudek, in an excellent paper, tried to explain all the congenital defects of the extremities, especially that of the fibula, by the assumption of the presence of a narrow amniotic sac, causing localized pull and pressure by adhesion. It has to be admitted that his explanation is able to clear up a number of facts, but it could, so far as I know, never be proved that there is such a thing as a tight amnion interfering with the growth of the extremities or amniotic adhesions leading to bowing of the bones. It has to be conceded that amniotic strangulation and amputation are possible, but that a dimple which is always at more or less the same place should be due to an amniotic adhesion which pulled on the extremity, brought about the bending of the tibia and disappeared, so that nobody has seen one, is more than I can conceive. Haudek examined one of the dimples histologically, and all other writers after him took his interpretation as proof that by pull of an amniotic band a chronic mechanical irritation was exercised on the skin, resulting in a chronic interstitial inflammation, with hyperplasia of the connective

12. Gaenslen, F. J.: Congenital Defects of Tibia and Fibula, Am. J Orthop. Surg. **12**:453, 1915.

13. Sperling: Zur Aetiologie der sogenannten intrauterinen Frakturen, Arch. f. Orthop. **1**:42, 1903.

tissue and atrophy of the glands and the subcutaneous fat tissue. I cannot follow this argument. The histologic section does not prove anything. I do not think even that a stain of the elastic fibers (which, when the question of a scar in the skin is concerned, is absolutely necessary) would be of great help.

I like to look at these dimples in a different light, basing my conclusions on the fact that they never have been proved to be real scar formations of the integument. They are seen frequently, but in none of the cases was an amniotic band still attached to the dimple. Furthermore, it is not so simple to understand why the supposedly tight and narrow amnion and the amniotic strands should so often interfere with the development of the extremities. It is commonly stated that once they start to develop the extremities form prominences on the surface of the body and on these the diseased amniotic membrane finds points of attachment. But with the same right one could expect insertions of amniotic bands on the head and back which, representing the convex part of the embryo, are closer to the membrane than the extremities. No localized lesion of the head or the back due to amniotic bands has been reported. The extremities, at the time when the adhesions are supposed to do their damaging action (fifth to eighth week of embryonal life), are more or less developing toward the concavity of the bent embryonal body, and there is no reason that they should be predilected points for amniotic adhesions.

If one examines a greater number of these dimples, one finds that they look more or less alike and that they are always related to a prominent portion of the skeleton. In cases in which there is bending of the tibia, the dimple occurs at the apex of the curve; in association with partial absence of the bone it occurs at the pointed end of the diaphysis of the affected bone. They look exactly the same as the dimple which one finds so frequently under normal conditions in the sacrococcygeal region and which is known as the fovea sacrococcygea. This dimple is at that place on the surface of the body where, before its curvature, the caudal end of the vertebral spine was connected with ligamentous connective tissue—the ligamentum caudale. It is possible that, just as the close local relation of a prominent skeletal portion to the embryonic skin results frequently in the formation of a funnel-like depression at this point, a congenital deformity of the extremities may produce a similar dimple. It is not an amniotic band which pulls on the extremity, but it is the deformed skeletal portion which sticks up against the skin and may become adherent to it. Later, when the skin develops in its different layers, especially if the layer of subcutaneous fat tissue appears, it elevates the skin from the adherent and scarred portion, which thus becomes a deeper or shallower dimple, depending on the

more or less marked adhesion of skin to bone. The histologic observations of Haudek [8] speak at least as much in favor of this supposition as of amniotic adhesions. Against amniotic adhesions speaks the fact that the superficial cutaneous structure of shallower dimples is perfectly normal, whereas in cutaneous scars one expects to find typical absence of the small field formation.

But what, if not amniotic adhesion and pressure, brings about the defects of the extremities and especially the characteristic bowing of the tibia? I have already mentioned that I consider more than anything else a faulty anlage of the extremity to lead to a disturbance of growth in a general way, resulting in dwarfism or gigantism of the affected limb, or to act by suppression of one or the other of the centers of ossification, giving rise to congenital defects. The exact mechanism by which the faulty anlage manifests itself, the pathogenesis of congenital deformities, is still unknown; it seems, however, that there is more than a disturbance of ossification. One gains the impression that in cases of more marked deformity the equilibrium which exists under normal conditions between the growth of the soft tissues and that of the skeleton has become disturbed. There can be no doubt that the relation of the musculature to the skeleton is of definite form-shaping influence. I mentioned this fact before, when I spoke of the frequently observed coxa vara associated with congenital defects of the femur. It is more than probable that there is a reciprocity between the growth in length of the skeleton and the expansion of the musculature and other soft tissues. They influence each other by their different stages of physical aggregation. The best example for this existing equilibrium is the fact that the tuberosity of the tibia with the insertion of the quadriceps tendon (patellar ligament) forms a unity with the upper tibial epiphysis, although from a purely morphologic standpoint one would expect the tibial tubercle to form a part of the diaphysis. But by the insertion of the patellar ligament in the epiphysis a bridging of the upper tibial epiphyseal plate by tendon tissue is avoided. The reason for this certainly is that the interstitial growth of the quadriceps tendon could not keep pace with the growth in length of the extremity in both epiphyseal plates around the knee joint. This alone shows how thoughtfully nature tries to keep up the balance between the growth of soft tissues and that of the skeleton. If this balance becomes disturbed, skeletal deformity must be expected.

If one looks up the notes of physical examination of patients with congenital defects of the leg, especially of those with bowing of the tibia, one almost constantly finds the presence of a tight achilles tendon and an equinous position of the foot. This tightness of the tendon seems to be more marked in these patients than in those with other

conditions, for instance, clubfoot. Recurrence following lengthening of the tendon, even if combined with posterior capsulotomy of the tibio-astragaloid joint, seems to be the rule. Operative findings in two of my cases showed that there was practically no tendon tissue but that the fibers of the gastrocnemius muscle were almost inserted into the os calcis, which represents an immature stage of muscle development. As a matter of fact, the clumsy appearance of the thickened and shortened limb, with the marked equinous position of the foot, resembles very closely the youngest stage in the embryonal development of the extremity, long before ossification takes place (the precartilaginous and cartilaginous stage of embryos from 1 to 2 cm. in length). It seems that in these cases not only the growth of the skeleton but that of the soft tissues has suffered, the musculature being much more affected. From the objective findings I conclude that, besides a primary faulty anlage, it may be the disturbed balance of growth in length between the muscles of the calf and the tibia which results in the deformity. If the muscles of the calf do not grow in length in the same amount as the tibia, they will form a tight string on the tibia. The tibia, which at this age is made up of highly plastic material, will have to adapt itself to the shortness of the muscles of the calf either by an anterior bowing or by decreased growth in length, or by both. The decreased growth in length may explain that in some cases of defect of the fibula the tibia is straight but considerably shorter (case 20). It may be straight but show a very clumsy shape (case 17), which is due to lack of differentiation. The bone has preserved its embryonal form to a considerable degree. The disproportion in length between the tibia and the muscles of the calf keeps the foot in its early embryonic equinus position.

The kink of the tibia in the middle third or at the junction of the middle and the lower third corresponds well to the apex of the curve, two fixed points of which are the insertion of the gastrocnemius muscle on the os calcis and the origin on the condyles of the femur, the knee joint being in flexed position (in utero). The kink has thus to be considered as caused by a chronic tension stress exercised on the tibia. From experiments with animals and from clinical observations, especially on bone grafts, it is known that chronic tension stress gradually leads to a zone of transformation of the bone which manifests itself as pseudo-arthrosis. It may be that the congenital pseudo-arthrosis of the tibia goes back to the same mechanism of imbalance of growth between the bone and the musculature, except that the tension stress in these cases would be more marked. Once the pseudo-arthrosis has developed and the fragments are overriding each other, the equinus

position of the foot will correct itself. Therefore, in cases of congenital pseudo-arthrosis pes equinus is rather the exception than the rule.

The congenital defect of the fibula is usually combined with an equinovalgus deformity of the foot. This deformity may be combined with a marked metatarsus varus, so that the diagnosis of congenital clubfoot is frequently made. There is lacking, however, the supination of the heel, and the deformity therefore should be considered as a combination of congenital clubfoot with deformity of the ankle due to the defect of the fibula (cases 13, 16 and 17).

The clubfoot component in these cases shows again how intrinsic the disturbance of the development of the extremity is and that endogenous etiologic factors have to be considered first.

The deformity of the ankle in cases of congenital defect of the fibula is often called in the German literature Volkmann's deformity of the ankle joint. Gaenslen introduced the term in the American literature. There does not seem to be anything specific about Volkmann's deformity of the ankle except the pronounced hereditary factor which he observed. He [14] (1873) observed the deformity in father and son; among seventeen members of the last three generations of the same family only ten were not affected. Males and females were evenly represented. Volkmann suggested the name hereditary congenital dislocation of the ankle joints, which was changed later by Bidder [15] to Volkmann's deformity of the ankle, because there is no real dislocation. A number of other cases have been reported, but only in a few was familial occurrence or inheritance of the condition demonstrable (Bidder, Mau [16]). The main factor in the deformity is the aplasia or hypoplasia of the fibula, with absence of the malleolar mortice. In a number of instances the fibula was fairly well developed but was displaced slightly backward and upward.

The deformity of the ankle was present in all my cases but was especially marked in case 18, in which, owing to the lack of the astragalus, complete lateral dislocation of the foot was present. The foot was a typical cleft or lobster foot, a rare condition associated with congenital maldevelopment of the fibula. I found in the literature only the case reported by Spiess.[17] The patient was a 36 year old man with absence of the fibula, shortness and bowing of the tibia and congenital disloca-

14. Volkmann, R.: Ein Fall von hereditärer kongenitaler Luxation beider Sprunggelenke, Deutsche Ztschr. f. Chir. **21**:538, 1873.

15. Bidder, quoted by Mau.[16]

16. Mau, C.: Beitrag zur Volkmannschen Sprunggelenkmissbildung, Ztschr. f. orthop. Chir. **48**:434, 1927.

17. Spiess, P.: Ueber kongenitalen Femurdefekt und verwandte Missbildungen, Arch. f. orthop. u. Unfall-Chir. **20**:234, 1922.

tion of the hip. The tarsus consisted of only two bones, one of which was the os calcis; the dentate of the other was questionable. Two metatarsal bones and toes were present. In my case a third rudimentary toe was present between the first and the fifth toe.

An even more marked deformity of the foot than that in case 18 was present in case 19, in which only the big toe had developed. There was complete absence of the fibula on the left side, whereas on the right except for posterior displacement of the lower end of the fibula the leg was well developed. Both peroneal tendons ran anteriorly to the external malleolus, and there was marked ankle valgus on both sides. This shows clearly that Volkmann's deformity of the ankle may be associated with complete absence of the fibula as well as with milder developmental errors, as, for instance, a simple backward displacement.

Besides the typical deformity of the ankle, the most common abnormalities of the foot are defects of the two lateral toes. In the cases of milder deformity this defect may be in the form of syndactylism or webbing of the fourth and fifth toes; in more advanced stages there is a fusion of the outer metatarsal bones and finally complete absence of the fifth or of the fourth and fifth toes. Of interest also is the fact that in case 19 the right foot showed syndactylism of the first and second toes. The end-phalanx of the first toe showed skeletal syndactylism, so that it is certain that the whole foot showed lack of differentiation, with complete absence of the two lateral toes. Other deformities, such as absence of tarsal bones and coalescence between the astragalus and the os calcis or between the os calcis and the cuboid are rarer.

In none of my patients with congenital defect of the fibula was inheritance of the condition demonstrable. This, however, should not be taken as proof against a vitium primae formationis and induce one to consider exogenous etiologic factors, such as amniotic constriction. It is a peculiar fact that more pronounced congenital deformities of the extremities are relatively rarely inherited. The milder forms, such as coxa vara, congenital shortness, syndactylism and clubfoot, show by far more frequently hereditary taint. An excellent example of hereditary occurrence of congenital deformity of the lower extremity can be seen in the following group of cases of defects of the tibia.

CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH LACK OF PROPORTION: DEFECTS OF GROWTH OF THE TIBIA

CASE 22.—The patient was a 2½ year old girl with marked deformities of both lower extremities. No other deformities had occurred in the family. Horizontal nystagmus was present. The femurs were well developed. The legs were very short, with angulation of the tibias forward and inward. Both feet were in marked

equinovalgus position. Abnormal movement of the knee joints was present, with subluxation on flexion. There was bilateral dislocation of the hip joints. Roentgenograms showed both hips to be dislocated. The tibias were formed by a clumsy short piece of bone with a sharp anterior edge, which was prominent in its middle. There was a small bony nucleus in the upper epiphysis of each of the tibias and another lateral nucleus in the soft tissue, most likely belonging to a deformed fibula. The bones of the feet showed normal development.

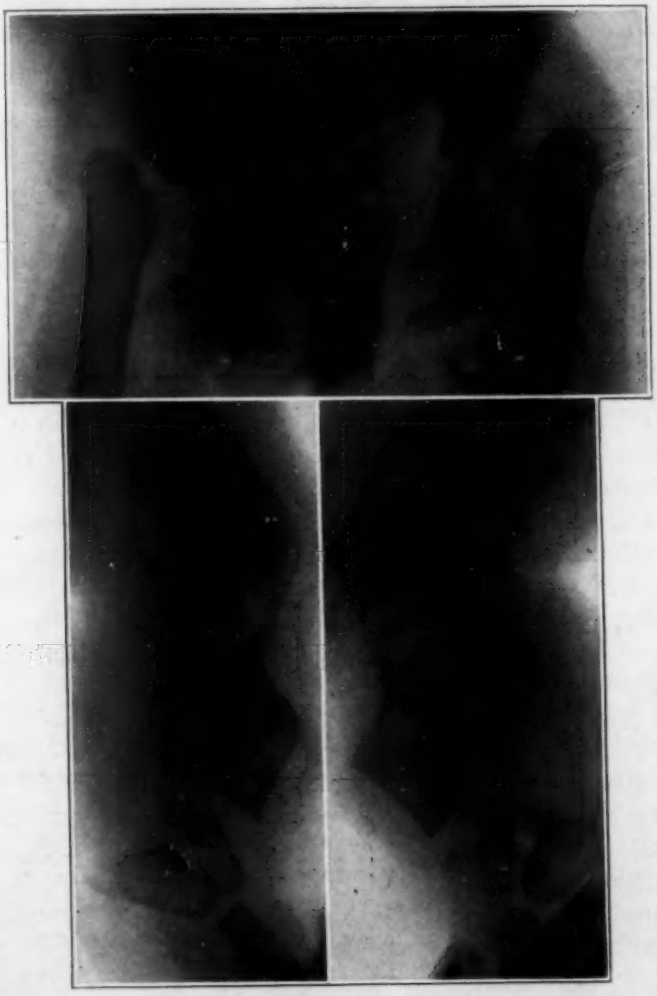

Fig. 22 (case 22).—Congenital dislocation of both hip joints, with deformities of the tibias and absence of the fibulas.

CASE 23.—The patient was a 2 year old boy, born with bilateral clubfoot, especially marked on the left. The inner side of the foot was bent upward, touching the inner side of the leg. A small dimple was present on the lower lateral aspect of the leg. The mother had a lobster hand. The ring finger was absent,

and its metacarpal bone was missing. There was a cleft between the third and the fourth finger, with a web at the base of the metacarpals. Two of three maternal cousins had similar deformities of the feet, and one had a cleft hand. Roentgenograms of the patient showed that in the left leg only the upper half of the tibia had developed; it ended with concentric atrophy. The fibula was well developed and was even thicker than normal. The foot was in extreme equinovarus deformity, but there was no intrinsic pathologic condition in the formation of the bones of the foot. The right tibia was much longer than the left, with

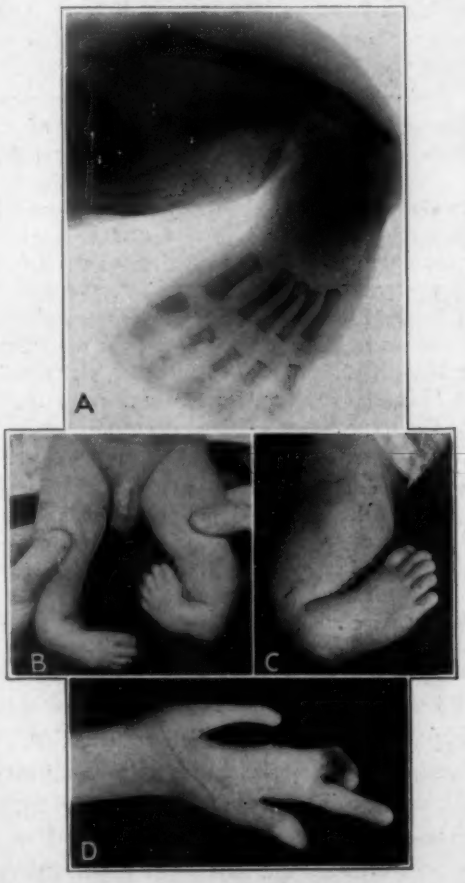

Fig. 23 (cases 23 and 24).—*A*, congenital clubfoot due to absence of the lower half of the tibia. *B*, hypoplasia of the fibula of the patient in case 23. *C*, congenital clubfoot due to absence of the lower half of the tibia in the patient in case 24. *D*, cleft hand of the mother of the patients in cases 23 and 24.

anterior and inward bowing. The fibula was thick and straight and apparently of normal length. The deformity of the foot was less marked; there was no involvement of the toes. Roentgenograms of the hand of the mother showed absence of the fourth metacarpal bone and finger. Some malformation of the carpal bones was present; the hamatum was absent.

Treatment.—For the first four months the deformity was treated by manipulation and casts and then by lengthening of the achilles tendon, with posterior capsulotomy. Wedge osteotomy of the fibula on the left foot was performed; the correction obtained was not very good. At the age of 1½ years the right foot was corrected by lengthening of the achilles tendon and by posterior capsulotomy, lengthening of the inner structures around the ankle joint (Brockman operation), astragalectomy, wedge resection in the calcaneocuboid region, osteotomy of the tibia and surgical union with the fibula to construct a mortice for the ankle joint. Good correction was obtained. Astragalectomy was also performed on the left foot with the Brockman operation with very little correction. Short leg braces were applied; amputation of the left foot was considered for a later date.

Case 24.—A 6 week old boy, brother of the patient in case 21, had been born with clubfoot on the right and absence of the lower end of the tibia. The fibula was present. A little dimple was present on the outer side, directly over the lower end of the tibia. The inner side of the foot almost touched the inner side of the knee. Roentgenograms showed absence of the lower half of the tibia, with hyperplasia of the fibula which pushed the foot into a marked adduction. The picture corresponded exactly with that on the left side of the patient in case 21. When the patient was 6 months old, the achilles tendon and the inner structures of the region of the ankle were lengthened, and good correction was obtained. Casts and a brace were applied. At the time of writing it is planned to split the lower half of the fibula in a sagittal plane and to transplant the inner half into the tibia in two stages, so as to form a malleolar mortice with growth in length in the transplanted epiphyseal plate.

Case 25.—The patient was a 1 month old boy, born with clubfoot on the right. No other congenital deformities occurred in the family. The tibia was 1 inch (2.5 cm.) shorter than it should normally have been. Roentgenograms showed absence of the lower epiphysis of the tibia, with considerable shortening. The fibula was of normal length and hyperplastic. The foot showed extreme equinovarus deformity, with marked hypoplastic changes of the big toe, the metatarsal bone of which was merely half the size of that of the second toe.

In the presence of so much hereditary taint as occurred in the two brothers (cases 23 and 24) it is clear that only endogenous factors can be of causative importance for the defect of the tibia. The mother has a typical cleft hand, two maternal cousins have clubfoot, and one has a lobster hand. I deal here with an inherited feebleness of growth of the tibia, which preserved more or less the shape of its precartilaginous and cartilaginous anlagen. In the first and second months of embryonal life the tibia is formed only by a cone-shaped mass. The reason for this lies in the fact that the cartilaginous preformation of the skeleton begins around the knee joint for the lower extremity; it extends the femur upward and the leg bones downward.[18] The thick proximal portions and the pointed distal portions can easily be recognized in the cases in which there is congenital absence of the lower end of the tibia,

18. Bardeen, in Fischel, A.: Lehrbuch der Entwicklung des Menschen, Berlin, Julius Springer, 1929, p. 786.

as is also the case with many congenital defects of the femur, which most frequently involve the upper end (the lower end in the tibia). The marked thickness of the fibula also points to this embryonal stage of development. It is clear that this thickness cannot be taken for a compensatory hypertrophy due to the maldevelopment of the tibia, as it is seen also in some cases of osteomyelitic destruction of the tibia. In

Fig. 24 (case 25).—Absence of the lower epiphysis of the tibia, with shortening of the leg. Hyperplasia of the fibula. Hypoplasia of the big toe.

these cases, the hypertrophy of the fibula develops under the stimulus of function, which is absent in the new-born. Up to the third month of life the fibula is evenly developed with the tibia; that is, it is relatively much stronger than the latter. In cases in which there is congenital defect of the tibia, it preserves its early thickness and appears hyperplastic. Thus, despite the fact that the deformities have to be consid-

ered as caused by faulty anlage of the extremities, certain embryonic stages may be recognized in different types of defects.

Better than the defects of the femur, the congenital deformities of the bones of the leg suggest a more extensive disturbance of growth than could be expected from a simple mechanical lesion, such as amniotic constriction. There is a complex disorder, involving the skeleton as well as the soft tissues of the extremities. It seems that the different parts of the extremity are in mutual dependency and that the more affected part will certainly alter the development of the other parts of

Fig. 25 (case 26).—Shortening of the left lower extremity, with posterior and valgus bowing of both leg bones, probably due to chronic bending stress in utero.

the extremity which primarily may have shown normal development. Therefore, there is always participation of the tibia associated with absence of the fibula, to a more or less marked degree, and vice versa, in instances of congenital defect of the tibia, the fibula does not develop to its normal shape but remains at an embryonal stage of hyperplasia. Experiments on young animals with suppression of growth of certain parts of the bones of the lower part of the front or hind legs will probably lead to a better understanding of this mutual dependency.

In the group of cases of congenital deformity of the femur, in which I considered the condition as entirely due to intrinsic factors damaging the development, I reported one case in which intra-uterine trauma was most likely; similarly, I report here a case of congenital deformity of the leg in which the condition also looks more like the result of an intra-uterine bending stress than a vitium primae formationis.

CASE 26.—The patient was a 6 month old girl, born with marked calcaneo-valgus. The dorsum of the foot rested on the anterior tibial aspect. The left leg was almost 1 inch (2.5 cm.) shorter than the right and showed lateral and posterior bowing of the tibia and the fibula. Roentgenograms showed marked shortening of the left leg, which was only two-thirds the size of the right. The entire diaphysis, however, had developed. At the junction of the middle and the lower third a kink was present in both bones, with an angle open anteriorly and laterally. No deformity of the foot was present. Treatment was by manipulation and a brace. Considerable improvement was shown within six months.

In this instance of congenital shortening of the leg, some narrowness of the intra-uterine cavity or the amnion sac must have brought the left leg into a pathologic position, resulting in the bending of both bones. The changes in these cases not only look different from real congenital defects but also react in a different way to conservative treatment. In case 13 as well as in case 24 simple conservative means, such as traction, manipulation and the application of a brace, were followed within a short time by marked improvement of the deformity. This shows that the trouble lay in the bone only and that there was no disturbance of the equilibrium of growth of the skeleton and the soft tissues.

ARRHENOBLASTOMA OF THE OVARY

TESTICULAR ADENOMA TUBULARE

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To Robert Meyer [1] belongs the credit for the chapter on the special ovarian tumors related to sexual characteristics. Contrary to the old concept that neoplastic cells are nonfunctional, he has pointed out that neoplastic cells may have a specific functional capacity affecting intimately the life of the patient and productive of profound changes in his or her sex life. He grouped these tumors under the following headings: disgerminoma, granulosa cell tumor and arrhenoblastoma.

A disgerminoma occurs either in the testis or in the ovary, and the two types closely resemble each other. The tumor is carcinomatoid and usually results in pseudohermaphroditism. It is said to arise from undifferentiated forms of germinal cells which have lost their faculty for sex determination. It is usually found in young girls presenting hypoplasia and underdevelopment of the genitalia. It may occasionally occur also in boys, and a group of tumors is usually present, lying in a lymphoid stroma.

The second, or feminizing, type—the granulosa cell tumors—may be cylindromatous or folliculomatous (von Kahlden) or may resemble a sarcoma. This tumor causes the secretion of excessive amounts of estrogenic hormones and therefore results in postmenopausal bleeding associated with endometrial hyperplasia. When it occurs in a child it is associated with marked sexual precocity. As the granulosa cell of the true follicles depends for its existence on the fully developed ovum, Meyer stated as his conclusion that it cannot become the forerunner of a granulosa cell tumor. This tumor is said to be derived from an embryologic rest in the medulla of the ovary (Popoff [2]).

The third type, the arrhenoblastoma, arises from undifferentiated germ cells that have retained their potency from epithelium of the testicular anlage or from cell rests in the hilus of the ovary. This type of tumor may cause defeminization: falling out of the hair, atrophy of

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Read in abstract before the Philadelphia Pathological Society.

1. Meyer, Robert: Tr. Am. Gynec. Soc. **56**:160, 1931.

2. Popoff, N. W.: Testicular Tubular Adenoma of the Ovary, Arch. Path. **9**:31 (Jan.) 1930.

the breasts, shrinkage of the opposite ovary, amenorrhea and sterility. It may be accompanied with signs of masculation: hirsutism and a change in voice (Emil Novak [3]). To be more specific, the rete ovarii and the medullary tubules (the anlage of the gonads) may under abnormal stimulation induce a masculine direction of development.

A subtype in this category of neoplasm is the adenoma tubulare testiculare, described by Pick,[4] to which our tumor belongs. In only a third of the cases does this tumor produce masculation. The degree of masculation may depend on the degree of atypical proliferation of atypical cells. The tumor with a rudimentary tubular structure is more prone to result in masculation (Taylor, Wolfermann and Krock [5]).

REPORT OF A CASE

E. O., a widow aged 52, was admitted to the Jewish Hospital on Jan. 28, 1934, with a provisional diagnosis of inguinal hernia on the right side and (?) tumor.

The patient was well until four years before admission, when a lump developed in the right lower quadrant of the abdomen in the inguinal region. It was about the size of a walnut and could be easily replaced. It had gradually increased in size, so that one year before the patient entered the hospital it was irreducible. About three months before her admission it became distinctly noticeable, protruding from the clothing and causing considerable pain and disfigurement. The patient complained of a persistent headache and some edema of the feet. She had never menstruated or had any vaginal discharge. She had been married and had indulged in sexual intercourse, with no lack of libido. There were no pregnancies.

The patient had measles when 6 years old and whooping cough when 12. No operations or accidents had been undergone.

The husband died of heart disease. There was no family history of tuberculosis, cardiac-renal disease, cancer or diabetes.

Physical Examination.—The patient was well developed and did not appear acutely or chronically ill. The skin was normal as regards color, texture and warmth. The patient was intelligent and cooperated readily. The voice was feminine in type. No hirsutism was noted.

The hands were normal in development and contour.

The pupils reacted to light and in accommodation and were equal and regular.

The veins of the neck were not distended. The cervical lymph glands were not palpable, and there was no tenderness or rigidity of the muscles. The thyroid gland was not palpable.

The breasts were small and pendulous. The supraclavicular and infraclavicular spaces were marked. Respiration and expansion were good and equal on the two sides. Tactile fremitus and vocal sounds were normal. Percussion revealed no abnormality. No râles were heard. The heart sounds were regular in force and rhythm and of good quality. There were no murmurs.

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3. Novak, Emil: Am. J. Surg. **23**:595, 1934.
4. Pick: Beitr. z. klin. Wchnschr. **17**:502, 1905.
5. Taylor, J. M.; Wolfermann, S. J., and Krock, F.: Surg., Gynec. & Obst. **56**:1040, 1933.

The liver and spleen were not palpable. No striae were present. There was no tenderness or rigidity. In the right inguinal region there was a large oval mass. It was not painful but was slightly tender on deep pressure. It was irreducible and fairly heavy. No gurgling was heard, and only slight fluctuation was noted. There was no sign of inflammation or edema.

Vaginal examination revealed a small but lax introitus, admitting two fingers. The vagina was short, measuring 3½ inches (9 cm.). It was smooth walled and ended blindly. No cervix, uterus, tubes or fornices were palpable. The clitoris was not hypertrophied.

A diagnosis of congenital absence of the uterus was made.

Operation (by Dr. Behrend).—Spinal anesthesia was employed. With the patient in the Trendelenburg position an incision was made on the right side about ½ inch (1.3 cm.) above Poupart's ligament and parallel to it. A large tumor in the right inguinal canal was carefully dissected out and found to be attached

Fig. 1.—Note the vaginal atresia depicted by the opaque solution, the smooth-walled outline of the vagina, the absence of a cervix and the triangular shape of the vagina. The pelvis is of the female type.

to the round ligament. The mass was clamped at the base, ligated and severed distal to the ligature with an electric cautery. The cut ends of the round ligament were sutured to the fascia of the transversalis muscle. The conjoined tendons were sutured to the shelving margin of Poupart's ligament.

Pathologic Report.—The mass consisted of an elliptical tumor, the size of a soccer ball, weighing 1,030 Gm. It was firm and on cross-section was seen to be composed of grayish fibers. The central portion of the tumor was of uniform structure. Some sections were more hemorrhagic than others.

Section of the tissue showed a large number of cuboidal epithelial cells having an alveolar arrangement. These glands resembled seminiferous tubules, many of them arranged in cords. The interglandular stroma contained a large amount

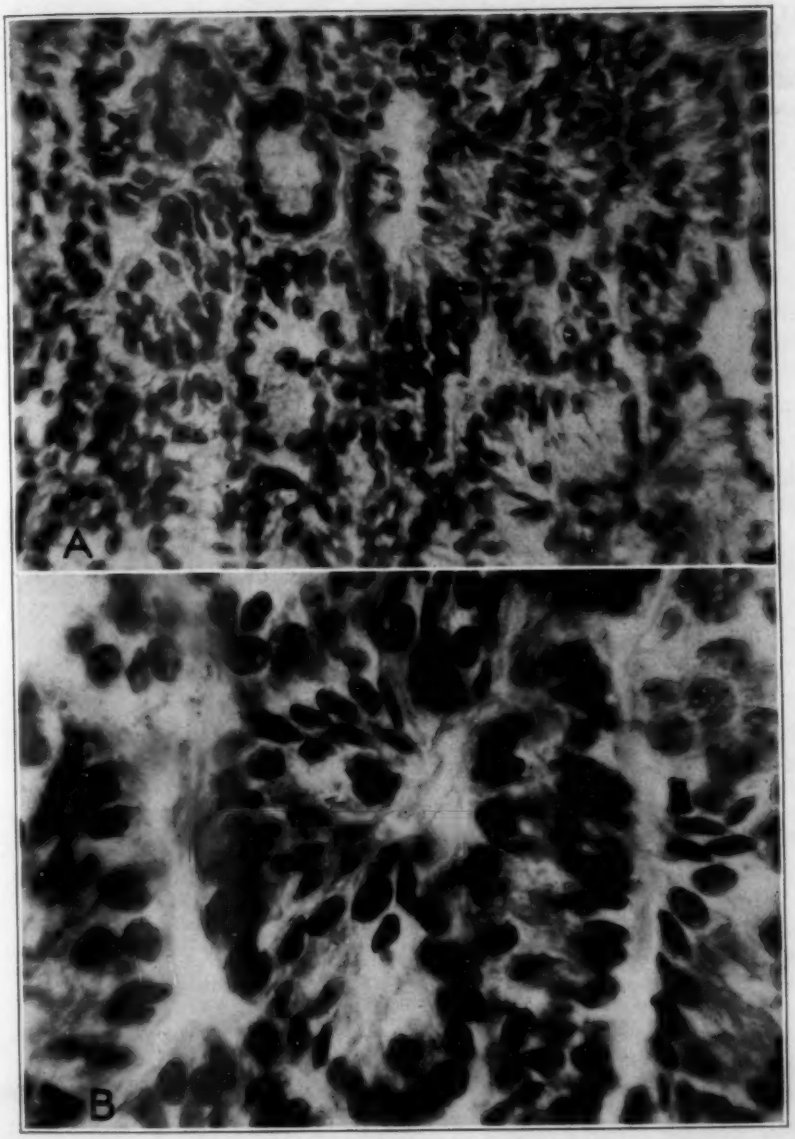

Fig. 2.—*A*, photomicrograph of a section of the arrhenoblastoma. Note the orderly arrangement of the epithelial cells about a lumen. There is a marked similarity to seminiferous tubules. *B*, section seen with the oil immersion lens. Note the lack of mitotic figures and the fairly homogeneous character of the cells.

of connective tissue and showed a moderate degree of hyalinization. Some of the fields presented infiltration by solid clusters of cells. No ovarian elements were observed.

The tumor represented a very rare type. According to Pick, such a tumor is derived from ovotestis. However, according to other authorities, it has its origin in the medullary cord, which is the embryologic parent of both the ovary and the testis. In a certain number of cases this type of tumor is associated with pseudohermaphroditism and hirsutism or infantile pelvic organs.

COMMENT

The relationship of arrhenoblastoma to intersexuality and pseudohermaphroditism must be very close. Consideration of this relationship also brings forth the question of sex determination. As Novak [6] expressed it, "Is a female a person with a primarily female zygote, or with an ovary, or one with the physical and psychic characters which one associates with a man?" Our case emphasizes that external feminine characteristics are not incompatible with a gonad containing testicular structures. As is well known, the other endocrine glands, such as the adrenal cortex, the pituitary body and the pineal gland, play an auxiliary though important rôle in sex differentiation and may well account for the lack of masculation in some cases of arrhenoblastoma. Thus, in X a case of pseudohermaphroditism in which feminine traits predominate, the only gonads present may be testes. It has also been pointed out that masculation in a person with arrhenoblastoma usually disappears with the removal of the affected ovary unless recurrence takes place on the opposite side (Moots [7]).

SUMMARY

A case of testicular adenoma tubulare of the ovary is reported. Masculine features were lacking, but other sexual anomalies were present, such as vaginal atresia, lack of a cervix, a rudimentary uterus and amenorrhea.

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6. Novak, Emil, and Long, J. Herman: Ovarian Tumors Associated with Secondary Sex Changes, J. A. M. A. **101**:1057 (Sept. 30) 1933.

7. Moots, C. W.: Am. J. Obst. & Gynec. **1**:864, 1921.

CHRONIC OCCLUSION OF THE PORTAL VEIN

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CHICAGO

The following case of chronic occlusion of the portal vein by an old organized and canalized thrombus is reported because (1) few articles have appeared in English on this subject, (2) the condition is rarely diagnosed clinically, usually being mistaken for cirrhosis of the liver, Banti's disease or ulcer of the stomach, and (3) in this case an unsuspected and unusual collateral circulation defeated the anticipated result of a successful splenectomy, which in any other case would have been the logical treatment.

The patient was an obese white woman 34 years of age. Two years before admission to the hospital she vomited about 1 quart (1 liter) of bright red blood. Since that time hematemesis accompanied with epigastric pain which radiated "from the back" had recurred at intervals of from three to four months. She fainted during two of these attacks. The last attack occurred about one month before her admission to the hospital.

At the time of the patient's admission to the hospital physical examination revealed no abnormality except a palpable spleen. She had been married for fifteen years. She had three children who were living and well. There were three miscarriages, the last in 1927 during an attack of influenza. In June 1927 the appendix and a "pus tube" were removed, and the perineum was repaired. In 1930 the patient noted bleeding from the umbilicus during menstruation. This was relieved by a plastic operation in 1931, at which time the uterus was amputated, and the cervix was repaired. The surgeon stated that at operation "a bloody jelly-like substance was spread over the genital organs" in an amount sufficient to fill his hands.

Roentgenograms of the gastro-intestinal tract were normal except for some shadows in the right upper quadrant of the abdomen which were suggestive of gallstones. The blood count showed: red blood cells, from 4,900,000 to 4,520,000; leukocytes, 5,700, and platelets, from 101,000 to 104,000. The bleeding time was three minutes, and the icterus index was 13.4. The Wassermann and Kahn tests of the blood were negative. The urine was normal.

The final clinical diagnosis was thrombocytopenic purpura, splenomegaly and gallstones.

On April 2, 1935, two weeks after the patient's first entry into the hospital, the spleen was removed. The operative notes were as follows: "The spleen is about double its normal size and weighs 500 Gm. or more. Old adhesions to the outer wall and diaphragm are highly vascular. The pedicle is short and contains enormous veins. The appearance of the splenic surface suggests old perisplenitis. The liver shows evidence of old periphepatitis, the right lobe being held to the

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diaphragm by dense adhesions. The pelvis is obliterated by old adhesions. The spleen was removed. Considerable blood was lost because of slipping of the splenic artery. A transfusion was given."

Two hours after the operation the blood pressure was 65 systolic and 45 diastolic. This was raised by the intravenous administration of fluids and by blood transfusions to 118 systolic and 90 diastolic. On the third postoperative day the patient's condition rapidly changed for the worse. The pulse and the respiratory rate were rapid. The abdomen was soft and neither tender nor distended. On the following day the pulse rate was rapid and thready, the temperature was high and the abdomen was distended. A roentgenogram "showed laddering of the small intestine indicative of paralytic ileus," and a stomach tube yielded fecal matter. The patient died early in the evening, about eighty-one hours after operation. It may be significant that albuminuria was present for the first time on the second postoperative day. As a result of transfusions and the loss of fluid by way of the stomach, the erythrocyte count rose to 5,520,000 on the second day. Just before the operation the platelets numbered 86,000; on the day of death, 190,000. On the day of death the nonprotein nitrogen content was 88 mg., and the blood sugar content, 192 mg., per hundred cubic centimeters.

After removal the spleen was considerably reduced in size by the escape of blood. It weighed 397 Gm., and after fixation it measured 5 by 10 by 15 cm. The capsule was not much thickened, but on the surface there were tags of torn adhesions. Two large severed veins were present in the hilus. Surfaces made by sectioning were dark red, the trabeculae were thicker and more prominent than normal and the splenic corpuscles were indistinct.

Microscopic examination showed that the splenic corpuscles were farther apart than normal, and there was relatively little change in them. Only rarely was a malpighian body noted with a small amount of hyaline fibrous tissue. Fibro-adenia was conspicuously lacking. The pulp exhibited diffuse fibrosis. The sinusoids were irregularly distended with blood. Scattered through the pulp were fairly numerous cells containing brown granular pigment. No nodules of siderofibrosis were observed.

Autopsy was performed two hours after death.

The anatomic diagnosis was recent splenectomy, hemoperitoneum, acute fibrinous peritonitis, paralytic ileus, ancient stenosis of the portal vein, a calcified periportal plaque at the hilus of the liver, interrupted collateral circulation by way of the splenic and left renal veins, thrombosis of the left renal vein and the veins of the collateral circulation, hyperemia of the left kidney and left adrenal gland, acute fibrinous pleurisy of the left side, multiple (three) superficial acute ulcers of the stomach, slight fat necrosis about the pancreas, a slightly patent ductus arteriosus, ancient appendectomy, hysterectomy and bilateral salpingectomy and fibrous peritoneal adhesions.

The body was that of an obese white woman. Between the umbilicus and the symphysis was an old white scar 17 cm. in length. On the left side of the abdomen was a recent curved incision 30 cm. in length.

There were fibrous adhesions between the right lobe of the liver and the diaphragm. The right end of the great omentum was firmly fixed by fibrous adhesions to the abdominal wall opposite the suprapubic scar; the left end was in the left upper quadrant of the abdomen at the former site of the spleen. The peritoneum was red, and the cavity contained about 700 cc. of bloody turbid fluid. The jejunum was greatly distended with gas, and the loops of intestine were loosely glued together by fibrinous exudate. The walls of the cavity left by the recent

removal of the spleen were covered with a red-gray exudate. Medially and posteriorly were the severed ends of four large blood vessels which had been closed with ligatures.

The heart, lungs, kidneys and gallbladder exhibited no gross pathologic changes. The ductus arteriosus (Botallo) permitted the passage of a small blunt probe. The veins at the lower end of the esophagus were visible by transmitted light but were not varicose. Except for three small superficial erosions in the gastric mucosa, the stomach and duodenum were normal in appearance. The liver was only slightly smaller than normal (it was not weighed because the whole specimen was kept intact for further study). Cut surfaces of the liver were yellowish brown, and the amount of periportal connective tissue in the triads appeared to be slightly increased. The cystic and common ducts were patent and of normal size. The pancreas was normal in appearance. In the fat above the head of the pancreas were about a dozen yellow-white nodules (foci of fat necrosis) measuring from 1 to 3 mm. in diameter. The left adrenal gland was hyperemic; otherwise these organs were unchanged. The right kidney weighed 130 Gm. The capsule stripped easily. The cortex was pale gray-brown and from 4 to 6 mm. thick. The markings were not normally distinct. The left kidney was slightly larger and darker red-brown than the right.

At a place 1 cm. above the origin of the portal vein the normal lumen ended abruptly, and the opening scissors entered a small tortuous channel which could not be followed. Serial transverse sections through the hepatoduodenal ligament upward to the hilus of the liver showed that the portal vein was replaced by a few small channels, up to 3 mm. in diameter, and filled with blood. Just below the hilus of the liver was a flat, curved calcified plaque, measuring 3 by 9 mm., apparently in the former wall of the portal vein.

The splenic vein had been ligated. It measured 2 cm. in diameter and was filled with a firm red thrombus.

The left renal vein measured 2.5 cm. in diameter and was filled with a mottled red and gray mass that reached to the inferior vena cava but did not extend into it. This thrombosis of the renal vein may have been the cause of the albuminuria which appeared on the second postoperative day. Four veins entered the left renal vein: the left ovarian vein, which entered from below and contained a solid red mass in its proximal 4 cm., and three large veins, each filled with a mottled red and gray thrombus, which entered from above. Two of these joined the renal vein 2 and 4.5 cm., respectively, from the hilus of the kidney. They followed a tortuous course upward, outward and slightly forward and united to form a single large trunk about 12 cm. (when measured after being stretched out) from the renal vein. The main trunk which was thus formed had been ligated at a place about 6 cm. (when straightened out) from the junction of the two veins just described. The third vein entered the left renal vein 6 cm. from the hilus of the kidney. It extended upward and lateral. It was joined by the left adrenal vein 1.5 cm. from the renal vein and proceeded along the pillar of the diaphragm for a distance (when straightened out) of about 12 cm., where it had been closed by a ligature. This collateral circulation is shown diagrammatically in figure 1.

Microscopic examination showed that in a transverse section through the hepatoduodenal ligament about the upper border of the pancreas (fig. 2) the thickened wall of the old portal vein was distinct. The vessel had been opened longitudinally; its former lumen was crossed by bands of dense fibrous tissue which divided it into irregular channels. At one place was a calcified mass attached to the inner surface of the original wall. Within the wall were numerous small spaces which represented dilated vasa vasorum. The lymph glands and nerves in this section were definitely outside the lesion just described.

In a section inside the hilus of the liver (fig. 3) there was a rich plexus of vessels which varied greatly in size and in the thickness of their walls. It was not possible to trace the outlines of the original branch of the portal vein in this section. Among the blood channels and vessels were numerous cross-sections of nerves. Above and to the right of the center was a focus of necrosis and lymphocytic infiltration. Along the lower left margin were several groups of proliferated bile ducts.

Figure 4 is a section of a triad located more deeply in the liver. Blood vessels were not as numerous as in sections nearer the hilus, but they were somewhat more abundant than normal.

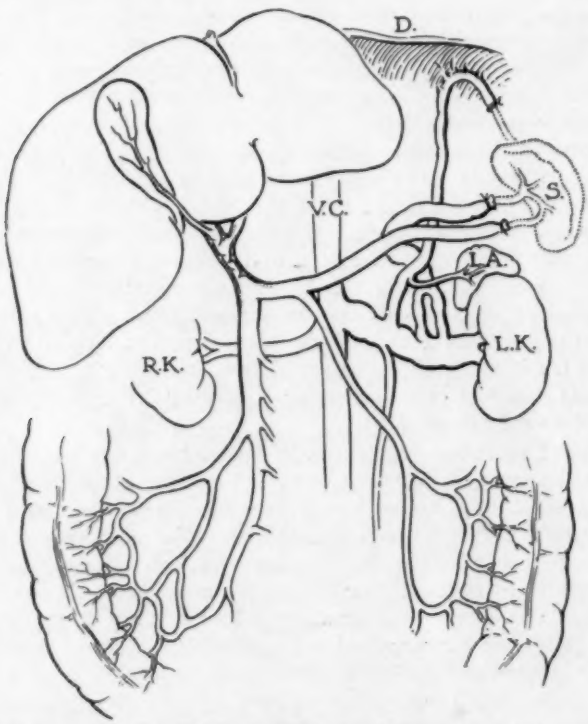

Fig. 1.—Diagram of the collateral circulation. The spleen *(S)* and the adjacent portions of the veins removed at operation are indicated by dotted lines. *L. K.* indicates left kidney; *R. K.*, right kidney; *V. C.*, vena cava inferior, and *L. A.*, left adrenal gland.

Summary of the Case.—An obese white woman, 34 years of age, suffered from epigastric pain and repeated gastric hemorrhages at intervals of three or four months for a period of two years. The spleen was palpable. These hemorrhages had not induced anemia, for the erythrocyte count one month after the last hemorrhage was 4,900,000. The platelet count ranged from 86,000 to 104,000 before splenectomy to 190,000 three days afterward. The leukocyte count was 7,500 before operation. Jaundice and ascites were significantly absent. The clinical diagnosis was thrombocytopenic purpura, splenomegaly and gallstones.

The spleen, after the escape of much blood, weighed 397 Gm. and showed diffuse fibrosis of the pulp but not the fibro-adenia of Banti's disease.

Autopsy revealed obliteration, canalization and partial calcification of the greater part of the main stem of the portal vein. At the hilus this condition gave place to a cavernous transformation or replacement of the vein which extended for a short distance into the liver. No satisfactory explanation of the repeated gastric hemorrhages was found. Varices were not present in the lower end of the esophagus, the usual

Fig. 2.—Transverse section (×7.5) through the portal vein at the upper border of the pancreas. One of the channels in the old vein has been opened longitudinally, and the sectioned edges of the wall are seen at the upper center. A calcified mass is attached to the inner surface of the old wall. Lymph nodes are seen at the left. Numerous small venous channels are visible in the old wall of the portal vein (enlarged vasa vasorum) and in the mass of fibrous tissue in the upper right corner.

source of hemorrhage in such cases. The collateral circulation, which was so adequate that ascites never developed, was by way of huge varicose venous connections between the splenic and the left renal vein. This exceedingly rare and unsuspected collateral circulation defeated the favorable results to be expected from splenectomy. Removal of the

Fig. 3.—Section (× 10.5) just inside the hilus of the liver, showing numerous venous channels and several arteries. Several nerves, cut transversely, traverse the mass. A little above and to the right of the center is an area of necrosis with lymphocytic infiltration. In the lower left portion of the field are many proliferated bile ducts. The liver is not fibrotic.

spleen and ligation of the splenic vein blocked the only open channel through which blood from the stomach and the intestinal tract could return to the general circulation.

THROMBOSIS OF THE PORTAL VEIN

Acute thrombosis of the portal vein is not uncommon. Lissauer reported 68 cases of portal thrombosis among 26,687 autopsies, and

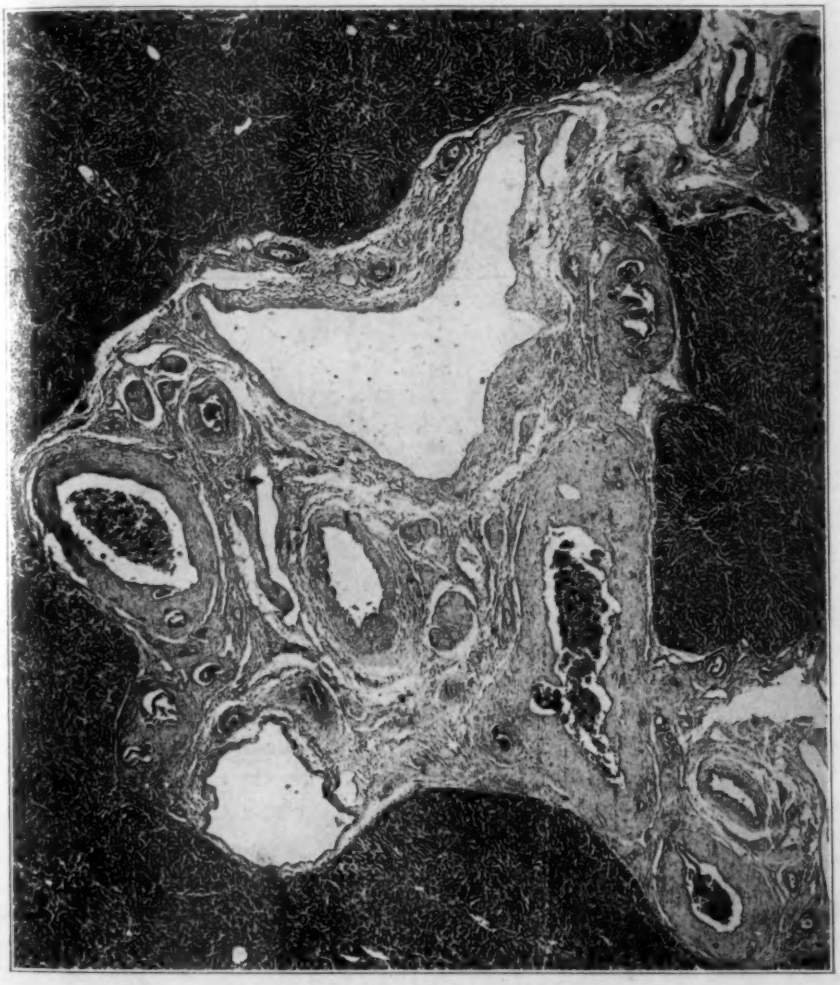

Fig. 4.—Section (×7.5) of a nearly normal triad located more deeply in the liver. There is no fibrosis of the liver.

Webster, 21 cases among 6,050 autopsies. The largest absolute number of cases in each report were associated with cirrhosis of the liver. The highest percentage of cases of portal thrombosis were associated

with swelling of the periportal lymph glands (46 per cent), abscess of the spleen (28 per cent), carcinoma of the pancreas (24 per cent) and primary carcinoma of the liver (11 per cent) in Lissauer's series and with cholangeitis (10.5 per cent) in Webster's series. Acute complete thrombosis of the portal vein usually progresses rapidly to a fatal termination from infarction of the small intestine, as pointed out by Josselin de Jong and others.

Chronic occlusion of the portal vein, on the other hand, runs a much longer course, up to twenty years or more (Wohlwill, case 1; Gruber, case 4; Risel, case 1; H. Gross, case 1; Pick; Hart, and Umber). The changes in the portal vein range from transformation into an impervious fibrous cord (Pippow) often with calcification, to replacement by an angiomatous or cavernous mass "the size of a goose egg" (Pick).

TABLE 1.—*Distribution of Patients by Age and Sex*

Age, Years	Group 1			Group 2			Grand Total
	Males	Females	Total	Males	Females	Total	
0-19	0	2	2	0	0	0	2
20-29	6	2	8	4	2	6	14
30-39	8	1	9	5	5	10	19
40-49	5	3	8	7	3	10	18
50-59	7	2	9	5	4	9	18
60-69	3	3	6	1	0	1	7
Not stated	(2)	(1)	13	0	0	4	17
Totals	31	14	55	22	14	40	95

This report is based on a study of the case here reported and the reports of 94 cases collected from the literature. Since some of the recorded case reports are too meager to be of much value, this fact is taken into account in analyzing the data. These cases may be divided into two groups: (1) those in which the portal vein was replaced by fibrous tissue with little or no canalization and (2) those in which the portal vein and/or its immediate vicinity was transformed into a cavernous mass of tortuous blood channels. This classification is significant because (1) the type of change has an effect on the clinical picture, (2) it influences the establishment of a collateral circulation and (3) it is a factor in determining the cause of death.

From table 1 it appears that chronic occlusion of the portal vein is about twice as frequent in men as in women. In all the cases included in this table autopsy was performed, but it was not possible to make corrections for the differences in the relative number of males and females in the total series of autopsies.

The most frequent symptoms and physical signs recorded were ascites, abdominal pain, hematemesis and a palpable spleen. The relative frequency of these symptoms and the causes of death are shown in table 2.

From table 2 several significant facts appear. Abdominal pain, usually located in the epigastrium but varying in intensity, duration and quality, was the most frequent symptom in each group. Ascites was much more frequently present in group 1. The same is essentially true of hematemesis. Loss of weight was present in from one fourth to one half of the patients in each group. Jaundice, usually slight, was observed with sufficient frequency to give it some diagnostic importance. The spleen was specifically stated to be palpable during life in a high percentage of cases; it was observed at autopsy to be sufficiently large to have been palpable in an even higher percentage. The most frequent cause of death in group 1 was gastric hemorrhage; in group 2, infarction of the intestines. The reason for the difference in distribution of ascites and hematemesis and the differences in the causes of death will be discussed later.

In 27 cases in group 1 no clinical diagnosis was given. Among the remaining 28 cases of this group, a correct diagnosis of thrombosis of the portal vein was given in 5 cases (Gruber, case 3; Kaspar, case 4; Hecht; Oppolzer, and Bruzelius and Key); a diagnosis of thrombosis of the portal vein or some other disease, in 4 cases (Achard; Leyden;

TABLE 2.—*Data on the Symptoms and the Causes of Death*

	Group 1					Group 2				
	Present	Absent	Percentage*	Not Stated	Total	Present	Absent	Percentage*	Not Stated	Total
Symptoms										
Ascites	40	7	85; 75	7	54	15	16	48; 37	9	40
Hematemesis	26	6	81; 47	23	55	23	8	74; 57	9	40
Abdominal pain	29	0	100; 53	25	54	27	2	93; 67	11	40
Icterus	11	12	48; 20	32	55	8	13	38; 20	19	40
Loss of weight	14	7	67; 26	34	55	13	7	65; 22	20	40
Spleen palpable	25	3	89; 45	27	55	14	1	93; 35	25	40
Spleen very large (post mortem)	32	..	84; 70	8	46	23	..	96; 77	7	36
Spleen normal or small	6					1				
Cause of death										
Hemorrhage	22	..	49	..	45	12	..	30	..	36
Intestinal infarct	9	..	20	..		16	..	44	..	
Other causes	15	..	33	..		8	..	26	..	
Unstated cause	..	..	..	..	10	..	..	..	..	4

* When two figures are given in this column the first is the percentage of cases in which the condition was present among the cases in which it was specifically mentioned; the second figure is the percentage of cases in which the condition was present among the total number of cases in the group.

Botkin, and Fleischhauer, case 2). Mention was made of ulcer of the stomach or duodenum in 7 cases, of cirrhosis of the liver in 6 cases, of Banti's disease in 4 cases and of pernicious anemia in 2 cases. In 10 cases in group 2 the clinical diagnosis was not mentioned. In this group the diagnosis was correct in only 4 cases (Gruber, case 4; Eppinger, case 32; Lommel, and Martin and Klages, case 3). The more common clinical diagnoses were ulcer of the stomach and Banti's disease (in 5 cases) and cirrhosis of the liver (in 4 cases). Other diagnoses included

such nonrelated conditions as syphilitic aortitis and dissecting aneurysm, myelogenous leukemia, sarcoma and tuberculosis of the spleen and thrombocytopenic purpura and gallstones. In 2 cases of fatal tuberculosis of the lungs (Loeb and Ehrentheil, case 3) the lesion of the portal vein characteristic of group 2 was an incidental observation at autopsy without symptoms referable to the condition during life. Kaspar stated that in only about 12 per cent of the cases of chronic thrombosis of the portal vein was a correct diagnosis made clinically.

ETIOLOGY OF THROMBOSIS OF THE PORTAL VEIN

Alterations in the composition of the blood, slowing of the blood flow and injury to the lining of the vessel have been accepted as the fundamental factors in the causation of thrombosis in general ever since the pioneer but thorough work of Cohnheim and of Welch. These factors play a part in thrombosis of the portal vein in several ways.

1. *Alterations in the Composition of the Blood.*—Polycythemia was present in at least 4 cases in this series. Kratzeisen, Gruber, Lommel, Versé and Emmerich each considered this a factor in his case. The erythrocyte count in Kratzeisen's case (also described by Gruber) was up to 6,500,000; in Lommel's case, as high as 10,000,000. Versé and Kratzeisen stated definitely that hematemesis did not occur in their patients; neither Emmerich nor Lommel mentioned hematemesis in the clinical histories. In the case here reported the red blood cell count was 4,900,000 one month after the last gastric hemorrhage. Kratzeisen and Gruber said they believed that the increased viscosity of the blood associated with polycythemia may well be a factor in thrombosis.

Marked thrombocythemia was present in the cases reported by Block and Klemperer. Rosenthal reported on thrombocythemia when the spleen was removed seven years before death in the case later reported on by Klemperer. At the time of operation the highest platelet count was 1,780,000. Rosenthal differentiated two types of Banti's disease: 1. In the thrombocytopenic type the platelet count is normal or reduced but rises temporarily immediately after splenectomy, with a quick return to normal. In cases of this type splenectomy gives favorable results. 2. In the thrombocythemic form of the disease splenectomy is followed by a long continued rise in the platelet count to as high as 1,000,000 per cubic millimeter, with a corresponding increase in the danger from thrombosis. Bryce also discussed this possible etiologic factor and reported on 2 cases of thrombosis of the splenic and portal veins, in one of which the platelet count after splenectomy was above normal (up to 700,000); in the other case thrombocytopenia was more marked than in the case here reported. Bryce emphasized the fact that in many cases enlargement of the spleen is associated with a low platelet

count and that after splenectomy in these cases the platelets often increase in number. He stated the conclusion that while thrombocythemia may not always be associated with thrombosis, it is an excellent criterion to use in determining the surgical risk of splenectomy.

2. *Alterations in Blood Flow.*—Changes in the blood flow as a result of intrahepatic obstruction constitute an important factor in the high incidence of thrombosis of the portal vein in atrophic cirrhosis of the liver. A further factor is the thickening of the wall of the vein, which, as pointed out by Weeber, is an almost constant accompaniment of cirrhosis and is probably due to the increased pressure in the portal vein. Thrombosis of the portal vein does not appear to be frequent in passive hyperemia of the liver and splanchnic region resulting from diseases of the heart. In the large series of cases of venous thrombosis associated with myocardial failure analyzed by Welch and by Sladen and Winternitz there was no case of thrombosis of the portal vein. Interference with the blood flow in the portal vein as a result of mechanical pressure by enlarged lymph glands and carcinoma of the head of the pancreas is a potent factor in thrombosis of this vein. In Lissauer's series 46 per cent of the patients with markedly enlarged periportal lymph glands also had thrombosis of the portal vein. Edens even stated that he considered that pressure on the portal vein by a distended stomach while the patient is lying on his back, as in taking an early afternoon nap, may cause sufficient circulatory interference to be a factor in the causation of thrombosis of the portal vein.

3. *Primary Changes in the Wall of the Portal Vein Capable of Inducing Thrombosis.*—These changes assume several forms. Phlebosclerosis, having many characteristics in common with atherosclerosis of arteries, is not infrequently observed as a primary disease of the vessel. The process begins in the intima and may progress to a stage in which there is extensive calcification. This condition was long ago cited as a factor in the etiology of thrombosis of the portal vein by Spiegelberg, Borrmann and Welch. Saxer, on the other hand, insisted that the phlebosclerosis is the result and not the cause of the thrombosis, because he had never observed the condition except in thrombosed veins. Later Buday, Hart, Winkler, Gruber and others showed that primary sclerosis of the portal vein does occur.

Phlebosclerosis is a degenerative process. Inflammation of the wall of the portal vein is usually secondary. That primary phlebitis or pylephlebitis of the portal vein also occurs has been pointed out by Lewis and Rosenow. Omphalogenic phlebitis in infancy was thought to have been a possible factor in case 4 reported by Gruber.

Pfifferling and Klemm were among the earliest authors to consider syphilis of the portal vein an important etiologic factor in throm-

bosis of this vein. Later M. Simmonds reported a larger series of cases and presented stronger evidence on the relation of thrombosis of the portal vein to syphilis of the wall of this vessel. The syphilitic lesion of the vein may be degenerative and affect the media, or it may be exudative and involve the other coats of the vein. It may be present alone or associated with typical gummas or syphilitic scars in the liver (Hart, Jastrowitz, Bülau, Loewenfeld and Borrmann). Simmonds' views have been accepted and confirmed by Ghon, Zinn, Wohlwill, Chiari, H. Gross and Falkenberg.

4. *Secondary Changes in the Portal Vein That May Influence Thrombosis.*—These changes are numerous and are chiefly the result of infection, but trauma is apparently a causative agent in some cases. This view was especially advocated by Heller, Schmorl, Ponfick, Borrmann, Köbrich, Wilke, A. Gross and Hecht. The patient reported on by Heller and Gross jumped from a height of 0.75 meter into a boat. Within ten minutes he became dizzy and fainted, and he afterward suffered from hematemesis and melena for several days. Death occurred after two years, from gastric hemorrhage, and at autopsy the portal vein was observed to be occluded by an old, completely organized and canalized thrombus. Other cases in which the condition was believed to have followed trauma were based on similar evidence of the *post hoc ergo propter hoc* variety. However, Heller, Köbrich and Wilke said that they believed that the presence of microscopic splitting of the elastic coat of the vein is confirmatory evidence of trauma.

Infections and other pathologic processes in the gastro-intestinal tract and spleen and abscess of the liver have been found associated with thrombosis of the portal vein. The frequency with which appendicitis leads to thrombosis of the portal vein has been emphasized by Fleischhauer, Ehrentheil, Lissner and Kuhr, each of whom has reported a case in which this etiology was probable. Otschkin said that he believed that in about 1 per cent of cases advanced appendicitis results in thrombosis of the portal vein. In his 1,692 cases of appendicitis there were 15 (0.9 per cent), and in 8,667 case reports collected by him there were 58 (0.67 per cent) cases in which appendicitis was associated with thrombosis of the portal vein.

Various acute infections have been held responsible for the thrombosis or, in the absence of any other obvious cause, have been considered as a possible or probable factor in specific cases: scarlet fever (Risel and Palmedo), pneumonia (Alexander), typhoid (H. Gross and Dock and Warthin, case 1), endocarditis (Goldmann), infection of the neck (Kratzeisen) and infection of the scrotum (Gruber). Even malaria has been mentioned as an antecedent disease (Ehrentheil).

Puerperal and other infections of the female genital tract have with greater reason been held to be etiologic factors in thrombosis of the portal vein by Rommelaere, Schulz and Müller, Block and others. Bucura collected reports of 12 cases from the literature and added 1 of his own in which thrombosis of the portal and/or the mesenteric vein occurred during pregnancy or the puerperium. Linzenmeier said he did not consider the portal system as a closed system and that thrombosis may extend directly, i. e., by continuity, from the veins of the uterus to branches of the portal vein. In my case the patient had an abortion and an operation for a "pus tube" eight years prior to death and six years before the onset of symptoms. Hysterectomy and salpingectomy were performed four years before death and two years before the appearance of the terminal clinical manifestations.

5. *Extension of an Inflammatory or Neoplastic Process from Surrounding Structures to the Portal Vein.*—This is an undoubted factor in many cases, e. g., enlarged periportal lymph glands (Lissauer), carcinoma of the pancreas (Kaspar), gallstone impacted in the common duct (Wurm), cholecystitis and choledochitis (Wurm, Alexander, Dock and Warthin, Wohlwill and Edens), chronic gastric and duodenal ulcers (Kaspar and A. Gross), pancreatitis and fat necrosis (Martin and Klages, Klages, Steinhaus and Edens), stone in the pancreatic duct (Chiari), chronic peritonitis with perivenous inflammation (Achard, Walker, Gohrbandt and Wohlwill) and foreign bodies and parasites (Wohlwill—a "worm" was removed from his patient's liver).

6. *Thrombosis of the Portal Vein Without Determinable Cause.*—The so-called marantic thrombi are instances of this type.

NATURE OF THE LESION IN THE PORTAL VEIN

The cases of chronic occlusion of the portal vein may be divided into two groups. In the cases in group 1 the vein was reduced to a fibrous cord with relatively slight canalization. In Pippow's case only did there appear to have been complete obliteration of the lumen of the vessel. In all the others the lumen was markedly narrowed and was frequently associated with one or a few narrow tortuous channels in the thickened wall. There is little if any question but that the condition in these cases was the result of organization and canalization of a mural or incompletely obturating thrombus of the portal vein. The extent of the lesion along the vein and its branches was determined solely by the extent of the original thrombus.

In the cases in group 2 the portal vein had been replaced by an elongated mass of spongy, cavernous tissue in which traces of the wall of the vein were usually, but not always (Pick, Hart and Meyer), discernable. This alteration occurred at any place between the junction

of the splenic and the mesenteric vein and the hilus or even extended deeply into the liver. In some cases this change was present also in the splenic vein. Concerning the nature of this lesion, there has been much dispute, and four views have been presented on the mechanism of its production, as follows:

1. The majority of those who have studied this condition have stated the belief that it is merely the result of organization of a thrombus with marked recanalization.

2. Versé, Risel, Emmerich and Josselin de Jong stated that in their opinion organization and recanalization of a thrombus in the portal vein are accompanied with a compensatory dilatation of the accessory portal veins of Sappey and the growth of telangiectatic granulation tissue in the hepatoduodenal ligament. It is therefore in the nature of an acquired anatomic anomaly.

3. Beitzke, Hart, Fleischhauer, Meyer, H. Gross and Benda stated that they considered the lesion a congenital malformation. Fleischhauer reproduced an illustration from Keibel and Mall's textbook of embryology to show the possibility of the development of such an anomaly by the atypical development of the plexus of veins between the omphalomesenteric and the hepatic vein during the second month of fetal life. He apparently considered that this plexus extended beyond the liver and met the portal vein at about the level of the head of the pancreas.

4. Pick argued strongly for the view that the condition is a neoplasm—an angioma or cavernoma of the hepatoduodenal ligament.

The difference in the extent of the cavernous transformation of the portal vein in different cases is one of the chief sources of disagreement as to the nature of the lesion. In the more marked cases the change patently exceeded that ordinarily seen in canalization of a thrombus, for it sometimes extended laterally far beyond the original limits of the vein itself. In Pick's case the cavernous mass was said to be "the size of a goose egg;" in Wohlwill's first case, the "size of a child's fist;" in Fleischhauer's case 2, "three fingers thick," and in Martin and Klages' first case, 10 by 15 mm. in diameter. The mass sometimes involved the entire portal vein from its origin at the confluence of the splenic and the mesenteric vein to its division into its branches at the hilus of the liver, as in the cases of Pick, Emmerich, Gruber (cases 2 and 4) and Ehrentheil (cases 1 and 2). The change was occasionally limited to the region of the hilus of the liver, as in the cases of Devé, Wohlwill (case 1) and Ehrentheil (case 5). It sometimes involved only a part of the vein—above the pancreas, as in Fleischhauer's case 2 and Gruber's case 1, or it was limited to the region of the pancreas, as in Falkenberg's case. In the majority of cases the cavernous tissue extended along the branches of the portal vein into the liver. In most instances this

extension was slight, up to 1 or 2 cm.; in a few cases, as in Ehrentheil's case 2, the change in the portal vein extended deeply into the liver. In the cases reported by Versé and Emmerich and in Ehrentheil's case 3 the cavernous change was present also in the splenic vein; in Gruber's case 3, about the mesenteric veins, and in Kuhr's case 2, in the pancreas. In 1 of the 2 cases in which the cavernous mass was largest the spongy mass invaded the liver only slightly, (Wohlwill's case 1), and in the other case (Pick) the change apparently stopped at the hilus.

In most of the cases in this group traces of the portal vein were still recognizable, at least by means of stains for elastic tissue, but no traces of the portal vein were recognizable in the cases reported by Pick, Beitzke, Hart, Meyer, Hulk, Cabred, Gruber (case 4), Josselin de Jong (case 8) and Martin and Klages (case 1). This fact was given great weight by Pick in his argument in favor of the neoplastic nature of the lesion.

In 18 cases nerves and lymph glands were observed within the cavernous tissue. Bile ducts also were present in the mass in the cases reported by Risel, Versé, Josselin de Jong (case 8) and Ehrentheil (case 5). The cavernous tissue extended into the pancreas in the cases of Versé and Ehrentheil (case 3).

Pick's reasons for believing that the lesion is a true neoplasm were as follows: 1. The mass was too large to be the result of organization and canalization of a thrombus; but the formation of telangiectatic granulation tissue, as suggested by Versé, might well have accounted for the massiveness of the lesion. This view was strengthened by the definite evidence of inflammatory changes about the portal vein in Gruber's case 2 and in Ehrentheil's cases 1, 2 and 4. 2. Pick stated that he considered the absence of any remnant of the portal vein as evidence of the neoplastic nature of the lesion, while Beitzke and others said they considered the lesion to be a congenital anomaly. Kuhr, however, insisted that as a result of chronic inflammation the wall of the vein could have been replaced by scar tissue. 3. The presence of nerves, bile ducts and lymph glands within the cavernous mass convinced Pick that the lesion was a tumor; it convinced Beitzke that it was a congenital anomaly and convinced Versé, Risel and others that it was an acquired anomaly. 4. Pick called attention to the fact that since cavernous hemangioma is known to occur outside the liver there is no reason that such a tumor might not be present in the hepatoduodenal ligament.

Perhaps the simplest explanation of the lesion is that its etiology varies in different cases. No one of the four theories just mentioned is satisfactory in all cases or explains all the clinical manifestations and pathologic features. If it is a tumor, it is difficult to explain the extension into the liver in so many cases and the limitation of the change to the

media of the vein in Falkenberg's case. Falkenberg suggested that if it is neoplastic it must be of the nature of a hamartoma or a choristoma. Kaspar and Falkenberg mentioned the difficulty of explaining the first appearance of symptoms late in life if the condition is congenital. Pick's case comes nearer to complying with the criteria of tumor than any other of the reported cases. Perhaps it will be necessary to accept his opinion, in spite of the doubts concerning it expressed by Kaufmann and many others.

COLLATERAL CIRCULATION

Pick has made a useful distinction between two types of collateral circulation in cases of obstruction in the portal area—the hepatopetal and the hepatofugal. When the circulation through the liver itself is unimpeded and the obstruction is limited to the portal vein, the hepatopetal circulation may compensate more or less completely by shunting the blood around the obstruction. This hepatopetal circulation is accomplished through numerous normal or anomalous channels which enlarge to accommodate the increased flow through them. In 8 of his 160 dissections (5 per cent) Walcker was able to demonstrate collateral veins, not vasa vasorum, accompanying the portal vein. More numerous and constant are the accessory portal veins of Sappey, which consist of "small vessels which arise in the folds of the peritoneum connected with the liver or which come from the stomach and pass either into the stem of the portal vein or directly into the substance of the liver." Specificially, they consist of (1) the deep cystic veins, from 15 to 20 in number; (2) the epiploic veins of the lesser omentum and the hepatocolic and hepatorenal ligaments; (3) veins of the hilus of the liver, the vasa vasorum of the portal vein and hepatic artery, and the veins in the wall of the common duct; (4) diaphragmatic veins; (5) veins in the suspensory ligament of the liver, and (6) the para-umbilical veins. Finally, the channels in the cavernous mass and in the canalized thrombus transmit blood to the liver from the abdominal viscera.

In portal cirrhosis of the liver the hepatofugal circulation shunts much of the blood from the abdominal viscera around the intrahepatic hindrance. McIndoe has classified the various parts of the hepatofugal collateral circulation into three groups on an embryologic basis: 1. The veins of group A are located at the two places in the gastro-intestinal tract where absorbing epithelium comes into contact with protective epithelium, i. e., at the cardia and at the anus. The veins at the cardia furnish an outlet to the superior vena cava and are best seen in esophageal varices. The veins at the anus provide an outlet to the inferior vena cava by way of the hemorrhoidal veins. 2. The veins of group B occur at the site of the obliterated fetal circulation—the para-umbilical veins in the falciform ligament of the liver. 3. The veins of group C

are found at all situations within the abdomen where the gastro-intestinal tract, its appendages or the glands developed from it become retroperitoneal developmentally or adherent to the abdominal walls as a result of some pathologic process.

Of the 55 cases included in group 1 in table 1, no statement was made concerning the collateral circulation in 15, and in 8 others the complete original article was not accessible. In the remaining cases there were 25 cases of esophageal varices, 1 case of esophageal and hemorrhoidal varices, 3 cases of hemorrhoidal varices and 1 case of varix in the stomach near the pylorus. In 2 cases (Schulz and Müller and Alexander) no collateral vessels were noted. In other words, the collateral circulation in 94 per cent of these cases belonged wholly or in part to McIndoe's group A. In 5 cases (17 per cent) collateral vessels passed also to the umbilicus and the veins of the anterior portion of the abdominal wall; these cases fall in McIndoe's group B. In 10 cases (32 per cent) there was additional collateral circulation that belonged to McIndoe's group C.

Among the 40 cases in my group 2, the collateral circulation was not described in 4, and the complete data were not accessible in 4. Only 17 of the remaining 32 patients had esophageal varices, and one had both esophageal and hemorrhoidal varices, and in 5 cases it was specifically stated that no esophageal varices were present. In contrast to the first group, only 56.3 per cent of the patients in group 2 had a collateral circulation of the type of McIndoe's group A, 3 (9.4 per cent) belonged in McIndoe's group B and 24 (75 per cent) in group C. This last figure is inaccurate in that it does not take into account the circulation through the cavernous mass itself, and this is an important part of the hepatopetal circulation in these cases. In Ehrentheil's cases 2 and 3 the cavernous tissue was the only detectable collateral circulation, and there was no ascites in either case. In 15 cases (47 per cent) an additional hepatopetal collateral circulation was specifically mentioned by references, for instance, to dilated veins of Sappey, adhesions between the stomach or duodenum and the liver or gallbladder.

When esophageal varices form an important part of the collateral circulation, they usually drain by way of the diaphragmatic, internal mammary, azygos and hemiazygos veins into the superior vena cava. It is extremely rare in a case of intrahepatic or extrahepatic obstruction of the portal veins to observe blood from the stomach and spleen reaching the inferior vena cava as in the present case. In a few cases (Fleischhauer, case 2; Klemperer, and Versé) there was drainage by way of adhesions in the left upper quadrant of the abdomen into the left renal or adrenal vein. In Lossen's case the celiac veins were markedly varicose and "extended downward and to the left about the left

kidney." The termination of these varicose veins was not clearly described. In Curschmann's case there was a communicating vein "as large as the little finger" between the coronary veins of the stomach and the left suprarenal vein.

I have been able to find in the literature reports of only 6 cases in which the collateral circulation was similar to that in the case here reported:

1. Tuffier. There was a communication between the splenic and the left renal vein.

2. Lejars. A large vein the size of a finger came off from the left renal vein and was connected by one branch with the plexus of the inferior veins of the diaphragm and by another larger branch which was lost in a postpancreatic plexus of veins which "communicated abundantly" with the splenic vein.

3. Mariau. There was a communication behind the pancreas between the splenic and the left renal vein.

4. Saxer. A huge varix in the wall of the stomach communicated with the splenic vein, and this, in turn, communicated with the left adrenal vein.

5. Pensa. There was an anastomosis between the splenic vein and the left renal vein.

6. H. Gross. The dilated splenic vein was continued by way of a wide channel through the substance of the spleen to its upper pole and thence by large varicose veins along the diaphragm to the left adrenal vein.

These 7 cases (6 previously reported) indicate the extreme rarity of this type of anastomosis. Gross, however, insisted that there is normally a communication between the splenic vein and the left renal vein by way of the left phrenic vein, which anastomoses with the veins of the diaphragm and these with veins in the capsule of the spleen. If this is true, it is evident from the infrequency of their being sufficiently large for detection that they do not often form a part of the hepatofugal circulation in cases of portal obstruction and cirrhosis of the liver. This is fortunate, as otherwise splenectomy would entail a prohibitive surgical risk.

CHANGES IN OTHER ORGANS

The most constant accompaniment of chronic occlusion or stenosis of the portal vein is enlargement of the spleen. The relative frequency of splenomegaly in the two groups is shown in table 2. The weight of the spleen was given in 29 cases, and the dimensions in centimeters, in 19 cases; in the remainder, information concerning the size of the spleen was entirely lacking or was stated only in general terms. In 3

(21 per cent) of the 14 cases in group 1 the spleen weighed more than 1,000 Gm., while in 6 (40 per cent) of the 15 cases in group 2 its weight exceeded 1,000 Gm. The largest spleen in group 1 weighed 2,150 Gm. (Mennet's case 1); the largest in group 2, 2,000 Gm. (Emmerich). The most frequent change in the spleen was fibrosis, in most cases diffuse and confined to the pulp. In a few cases it showed the fibro-adenia characteristic of Banti's disease. Chronic perisplenitis, ancient and recent infarcts, sclerosis and thrombosis of the splenic vein were frequently recorded.

Changes in the liver are not as extensive or as frequent as might be supposed. The weight of this organ was given in only 28 cases (12 in group 1 and 16 in group 2). One half or more of the livers in these cases weighed less than 1,500 Gm. Boyd has shown that the median weight of the liver of men between the ages of 25 and 55 ranged

TABLE 3.—*Data on the Weight of the Liver*

	Group 1		Group 2	
Weight of Liver, Gm.	Number of Cases	Percentage	Number of Cases	Percentage
750- 999	2	16.6	1	6.2
1,000-1,249	4	33.3	2	12.5
1,250-1,499	3	25.0	5	31.3
1,500-1,749	1	8.3	7	43.7
1,750-1,999	1	8.3	0	0.0
2,000-2,249	0	0.0	1	6.2
2,250-2,500	1	8.3	0	0.0
Totals	12	99.8	16	99.9

from 1,820 to 1,840 Gm., while the median weight of women aged between 20 and 60 fluctuated between 1,460 and 1,430 Gm. The weights in the 28 cases in the two groups in this series are shown in table 3. In approximately 75 per cent of the cases in group 1 the liver weighed less than 1,500 Gm., and in 50 per cent of the cases in group 2 it weighed less than 1,500 Gm. It appears probable, therefore, that the hepatopetal circulation through the cavernous tissue at the site of the portal vein in the cases in group 2 was a factor in maintaining the nutrition of the liver. In the greatest number of cases the reduction in the size of the liver was apparently due to simple atrophy (Saxer, Pick, Buday and Kretz); in a smaller number there was moderate fibrosis, usually associated with an extension of the lesion in the portal vein into the liver; in only 7 cases in group 1 and in none in group 2 was there actual evidence of cirrhosis. In 11 of the 24 cases in group 2 in which the hepatic artery was mentioned it was specifically described as dilated. Such a change in this artery was mentioned in only 1 case in group 1. Several authors said that they considered the dilatation of the hepatic

artery as a compensatory process. If it is, then the rarity of this arterial change in group 1, in which the flow through the portal vein was interfered with as much as or more than in group 2, is difficult to understand.

Definite syphilis of the liver with gummas and marked scarring was present in the cases of Hart, Jastrowitz, Bülau Löwenfeld and Borrmann. Chronic adhesive perihepatitis was frequently observed. Proliferation of the bile ducts was recorded by Risel and Chiari and in the description of my case (fig. 3). Infarcts of the liver were mentioned by Lommel, Ehrentheil (case 4) and Kaspar (case 3). Changes in the liver sometimes produced a marked asymmetry in the organ, such as disproportionate atrophy of one lobe (Klemperer) or hypertrophy of the caudate and/or quadrate lobes (Hecht and Martin and Klages). Gallstones, the possible relation of which to the lesion in the portal vein has been mentioned, were present in 7 cases (Alexander; Mennet, case 2; Gruber, case 4; Dock and Warthin, case 1; Hart; Falkenberg, and Emmerich).

An interesting and possibly significant observation was that of adenoma of the liver. The lesion was recorded in only 1 case in group 1 (Kaspar, case 4, and Umbreit, a doubtful case), but in 5 and possibly 6 cases (12.5 per cent) in group 2 (Risel; Kuhr, case 1; Klemperer; Meyer, and Hulk). In 1 case described by Martin and Klages (case 2) "small nodules" were present in the liver but were not further described or identified. The rather surprisingly high incidence of these adenomas has led to differences of opinion as to their origin and significance. Hulk said that they are present only incidentally; Meyer said that they, like the change in the portal vein, are malformations, while Risel and Klemperer said that they result from regenerative processes at the site of former foci of structural damage to the liver.

Acute or chronic gastric and duodenal ulcers were associated lesions in the cases reported by Bode, Kaspar, Gruber and Klemperer.

Numerous related or merely coincidental changes in the pancreas have been recorded: fat necrosis (Edens; Dock and Warthin, case 2; Wurm; Emmerich; Simmonds, and Martin and Klages, case 1), fibrosis or chronic pancreatitis (Chiari; Alexander; Falkenberg; Meyer; Wurm; Fleischhauer, and Eppinger, case 32, associated with diabetes), stone in the pancreatic duct (Chiari), thrombosis of the pancreatic veins (A. Gross, Wilke, Gruber, Köbrich, and Martin and Klages), involvement of the pancreas in the cavernous tissue about the portal vein (Falkenberg; Versé; Meyer; Gruber, case 1; Kuhr, case 2, and Ehrentheil, case 3) and ectopic pancreatic tissue, which Meyer said he thought was evidence in favor of his view that the cavernous lesion in the portal vein is a malformation.

RELATION OF SYMPTOMS TO THE LESION

In the preceding paragraphs there have been presented (1) the chief symptoms of chronic obturation of the portal vein, (2) the nature of the two types of pathologic process encountered in this vein and (3) the pathologic changes in other organs associated with this condition. It is now possible to explain the symptoms on the basis of their underlying structural changes and to make clear the difference in distribution of symptoms and causes of death in the two groups of cases and the variable clinical picture within each group.

Epigastric pain is an almost constant, and usually the earliest, symptom. This pain is only rarely excruciating and is frequently described merely as "epigastric distress." It is irregularly intermittent; it has no definite relation to the taking of food, and it generally precedes or accompanies gastric hemorrhage, as in my case. It is logical to conclude, therefore, that the pain in this condition is on an anatomically and physiologically different basis from that of gastric and of duodenal ulcer. The pain in chronic thrombosis of the portal vein is probably related to pressure from the esophageal varicose veins, to dilatation and stretching of the veins distal to the obstruction and/or to involvement of nerves in the scar tissue or the cavernous tissue about the lesion.

Hart said he was convinced that chronic thrombosis of the portal vein is a much more frequent cause of gastric hemorrhage than is generally believed. Its apparent infrequency is due to the fact that routine examination of the portal vein is too rarely made a part of postmortem examinations. Gastric hemorrhage occurred slightly more frequently in the cases in group 1. When present it was usually the result of rupture of an esophageal varix. In Devé's case the hemorrhage was from the varix near the pylorus; in other cases, from hemorrhagic erosions or acute superficial ulcers of the stomach or duodenum (Klemperer and Simmonds). The frequency and periodicity of hematemesis was variable. Occasionally it was the first symptom and was quickly fatal, although the lesion in the portal vein discovered at autopsy was of many years' standing (Hart; Pick; Chiari; Umber; Wurm; Kuhr, case 2, and Ehrentheil, cases 1 and 4). In the cases of Falkenberg and Lossen gastric hemorrhage occurred at the beginning of the clinical manifestation but did not recur, although these patients survived for two and twelve years, respectively, after the onset of symptoms. In other cases periods of frequent hematemesis were separated by years of freedom from this symptom. H. Gross' second patient had gastric hemorrhages forty-one and thirteen years before death; Kaspar's second patient had hemorrhages seven years before death, and A. Gross' patient, two years before death. In other cases hematemesis recurred at frequent intervals over long periods of time (in Gruber's cases 3 and 4

for eighteen and twenty-seven years, respectively; in Kuhr's case 1, for from eight to eleven years). In Loeb's case and in Ehrentheil's case 3 there were no symptoms referable to the abdomen, and the lesion of the portal vein was observed incidentally at autopsy.

In 11 cases in which hematemesis was definitely stated to have been absent (Loeb; Emmerich; Kratzeisen; Josselin de Jong; Lommel; Eppinger; Schulz and Müller; Martin and Klages, case 2; Wohlwill, case 1; Ehrentheil, case 3, and Gruber, case 2), only 2 (Gruber and Martin and Klages) were observed at autopsy to show esophageal varices. Only 1 of these 11 cases, that of Schulz and Müller, belonged in group 1. It is evident, therefore, that the hepatopetal circulation through the cavernous tissue that was characteristic in group 2 was a factor in preventing the establishment of a hepatofugal circulation through the veins at the lower end of the esophagus. Since the hepatopetal circulation is less well established in group 1, esophageal varices are more frequent in that group. This accounts for the higher mortality rate from hemorrhage in group 1 (table 2).

On the other hand, the marked tortuosity of the blood channels in the cavernous tissue characteristic of group 2 slows the blood stream and thus favors thrombosis. This, in turn, explains the higher incidence of death from infarction of the intestines in group 2.

Ascites was much more frequent in group 1 than in group 2 (table 2). The presence or absence of this symptom depends on the adequacy of the collateral circulation. Ascites occurs in three variant forms: (1) recurring over a period of years—Beitzke, seven years; Kuhr (case 1), eleven years; Mennet (case 1), seventeen years; Fleischhauer (case 1), nineteen years; (2) persistent for several years—Buday (case 2) and Gruber (case 3), each one year; Schulz and Müller, two years; Goldmann, four years; Ehrentheil (case 5), five years, and Gruber (case 4), six years, and (3) late, i. e., with the first occurrence less than one year before death. The six cases of the third form of variant were as follows:

	Total Duration of Symptoms	Ascites
Kratzeisen	5 to 11 years	5 or 6 weeks
Pippow	6 months	6 weeks
Umber	20 years	2 months
Eppinger	7 years	5 months
Buday (case 1)	7 months	7 months
Falkenberg	2 years	8 months

These variations in ascites as a symptom are related to the collateral circulation. In the recurring form the circulation periodically shows decompensation, in the persistent form it is never entirely competent and in the terminal or late form there is sudden and complete decompensation. As pointed out by Martin and Klages, rapidly developing

ascites is of grave prognostic significance. Any one or more of the other symptoms may vary with complete intermissions, a fact emphasized by Risel.

SPLENECTOMY IN CHRONIC OCCLUSION OF THE PORTAL VEIN

Splenectomy was performed in 5 cases in this series. The length of survival after this operation in each case was as follows: Klemperer, seven years; Kratzeisen, five months; Martin and Klages (case 1), five weeks; Simonds; three days, and Lossen, not stated. The infrequency with which the spleen is removed in this condition is surprising, for this would seem to be the logical treatment. Burton-Opitz, in careful experiments with a *Stromuhr,* determined that in the dog 21 per cent of the portal blood comes from the spleen, and W. J. Mayo has stated that splenectomy reduces by 20 per cent the amount of flow through the portal vein. This operation therefore reduces the burden on the collateral circulation by about one-fifth, probably more when the spleen is greatly enlarged. The reasons for the infrequency of splenectomy in chronic occlusion or stenosis of the portal vein are probably (1) the rarity of a correct clinical diagnosis (Kaspar), (2) the risk of serious or even fatal hemorrhage in the separation of perisplenic adhesions which are present in about 75 per cent of the cases, (3) the known danger that thrombosis of the stump of the splenic vein will extend into the portal vein and cause death from infarction of the intestine and (4) the statement of W. J. Mayo that 10 per cent of the patients with splenic anemia who survive splenectomy die within ten years from gastric hemorrhage. However, it may be remarked that patients with chronic occlusion of the portal vein survive for a period of from only a few months to two or three years once the collateral circulation has become so incompetent as to give rise to rapidly increasing ascites or the esophageal varices have become so large as to be the source of frequent copious hemorrhage.

SUMMARY

A case of chronic occlusion or stenosis of the portal vein is reported in which the favorable results which might have been expected from splenectomy were defeated by the presence of an unsuspected and exceedingly rare type of collateral circulation, namely, a large varicose communication between the splenic and the left renal vein.

Chronic thrombosis of the portal vein occurs in one of two forms. A mural or incompletely obturating thrombus is either organized with relatively little or no recanalization or the vein and adjacent tissue are transformed into a cavernous or angiomatous mass. There is a sharp difference of opinion as to whether the cavernous or angiomatous type is

the result of thrombosis or a malformation or is a true neoplasm. These two forms differ, relatively, in symptomatology and in the mode of death produced.

The American and English medical literature contains few references to the subject of chronic occlusion of the portal vein, although this lesion occurs with sufficient frequency to justify its consideration in the differential diagnosis of all obscure cases of gastric hemorrhage or ascites.

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FIBROSARCOMA OF THE SOFT PARTS

WITH SPECIAL REFERENCE TO RECURRENCE AND METASTASIS

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The question of the choice of treatment for sarcoma of the soft parts is constantly recurring, with proponents of radical or conservative surgical intervention and of irradiation. In an effort to answer this question in part, the study reported on here was undertaken. Among the reports of fibrosarcoma of the soft parts in the files of the pathologic laboratories of the Huntington Memorial Hospital and the Palmer Memorial Unit of the New England Deaconess Hospital, records of one hundred and sixty-three cases were found with adequate clinical data for careful study. In many other cases sarcoma had been diagnosed, but either the follow up or the history was unsatisfactory.

The follow-up period for the living patients ranges from thirty-one years in one case to ten months for a patient operated on in 1934 and included because of the interest of the case. The great majority of patients have been followed to death or for at least three years. Three cases without follow up are included because of special features.

Seventy-two per cent of the living patients have been followed for three years or over from the onset of their disease. Of the entire group, seventy-two died, sixty from disease and others so soon after the last treatment that the probability that disease was still present was great.

The tumors represent a fair cross-section of fibrosarcoma as encountered in practice, since the cases comprised not only those of patients referred to the Huntington Memorial Hospital and the Palmer Memorial Hospital but many observed by physicians throughout the Commonwealth in their private practice and in the surgical material sent in for diagnosis to the State Tumor Diagnosis Service. One advantage of this type of material is that the tendency is toward exclusion of the cases of advanced fibrosarcoma, in many of which naturally the patient is hospitalized, especially in those institutions known for the treatment of cancer. No selection has been made of the cases other than to choose those in which an adequate history and follow up could

From the Laboratories of Pathology of the Harvard Cancer Commission and of the New England Deaconess Hospital, and the Department of Pathology, Harvard University Medical School.

be obtained. Many physicians of Massachusetts have given time and effort to making these data available.

So often and so falsely is sarcoma said to be a disease of young persons that we present table 1, which shows a wide distribution of patients according to age. The age given is the age at the onset of symptoms. The distribution centers in the sixth decade, the mean age at the onset being 49.1 years for males and 50.4 years for females. This is about ten years younger than the average age at death from cancer of all types in Massachusetts, which is 59.3 years for males and 61.5 years for females.[1] Figure 1 is a graphic comparison by age groups of our patients and those in a random series of consecutive patients with carcinoma verified by autopsy. While sarcoma is more frequent in persons of the younger age groups, the distribution is not far different than that for carcinoma.

The distribution according to sex is fairly even.

TABLE 1.—*Distribution of Cases According to Age and Sex*

Age in Years*	Male	Female
0- 9	1	1
10-19	2	1
20-29	7	6
30-39	11	10
40-49	15	19
50-59	12	22
60-69	15	13
70-79	9	8
80+	1	2

	Mean	Standard Deviation	Standard Deviation of Mean
Male	49.1	±17.0	±2.0
Female	50.4	±15.4	±1.7

* The age was unknown in 8 cases.

One of the difficulties in treating fibrosarcoma early is that, as in the case of other malignant tumors, pain is not an early symptom, and consequently patients do not come promptly for relief. Swelling is usually the first sign to attract the patient's attention, and in many cases in the earlier stages the condition is superficial. For some time the tumor may be freely movable, and as a rule it becomes attached to the overlying skin before it does to the underlying structures. In thirty-five of our cases the tumor was definitely intracutaneous or subcutaneous. In some instances the contour is so well defined as to give a suggestion of encapsulation, and in other instances the tumor becomes thinned and spreads diffusely into the surrounding tissue. Examination of the gross specimen usually shows a pale, fibrous, somewhat infiltrating tumor, ordinarily tending to expand the surrounding

1. Bigelow, G. H., and Lombard, H. L.: Cancer and Other Chronic Diseases in Massachusetts, Boston, Houghton Mifflin Company, 1933, p. 264.

structures, with varying degrees of vascularity. Necrosis is not nearly so marked a feature as in the case of epithelial tumors. The masses are usually resilient and are sometimes almost translucent, owing to edematous portions. Hardness, which is a marked feature of carcinoma, is frequently absent in fibrosarcoma, and when it does occur it yields to local pressure rather than offering the mass resistance of carcinoma.

So far as can be determined from the records, trauma is not an appreciable factor as an initiating agent. This is in keeping with Ewing's [2] findings in his recent report on the relation of tumors to trauma.

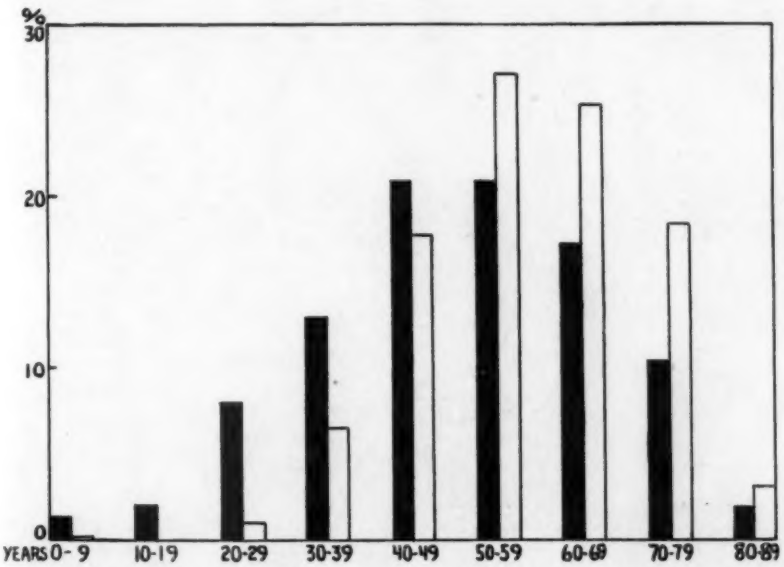

Fig. 1.—Graph showing distribution of fibrosarcoma and of carcinoma according to age. The solid black blocking indicates sarcoma; the white blocking, carcinoma.

In reviewing the older slides it is of interest to note that some of the tumors recorded as fibrosarcoma in the files were found to be atypical granulation tissue or a focus of localized fibrosis. In the cases of this type that could be followed recovery was uniformly the rule, helping to reenforce the diagnosis of a benign lesion. Sclerosing hemangioma is also a confusing lesion. It is our impression that a diagnosis of fibrosarcoma is made erroneously more frequently than true fibrosarcoma is classified as a benign lesion.

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2. Ewing, J.: Modern Attitude Toward Traumatic Cancer, Arch. Path. **19:** 690 (May) 1935.

In most instances the tumor was treated by operation, which varied from local to radical excision; in the case of tumor of the extremities the latter was sometimes amputation. A small proportion of patients received postoperative treatment with the roentgen rays and radium, in all instances without any notable influence on the course of the disease. In several instances recurrences progressed in spite of active radiation therapy. It is of interest to note that among five cases in which the tumor was associated with definite irritative stimuli of one type or another, in two the growth followed roentgen or radium treatment of

TABLE 2.—*Types of Treatment of Fibrosarcoma*

		Operation	Operation; Roentgen Rays	Palliative	Operation; Roentgen Rays; Radium	Roentgen Rays	Radium; Roentgen Rays	Radium	Operation; Amputation; Roentgen Rays	Operation; Coley's Toxins	Radical Operation	No Treatment
Fibrosarcoma	Head	6	..	..	..	..	2	1	..	..	..	1
	Trunk	4	1	..	..	..	..	..	..	..	..	..
	Intra-abdominal region	2	2	1	..	..	..	..	..	..	..	1
	Extremities	17	..	..	..	..	..	..	1	1	..	..
	Special cases	2	..	..	..	1	..	..	..	..	..	..
Neurogenic fibrosarcoma	Head	7	..	..	..	..	..	..	..	..	..	..
	Trunk	13	2	..	..	..	..	..	..	..	..	1
	Intra-abdominal region	1	..	..	1	..	..	..	..	..	..	1
	Extremities	12	..	..	..	..	..	..	..	..	..	..
Fibrosarcoma with tumor giant cells	Head	3	1	..	..	..	..	1	..	..	..	1
	Trunk	6	1	..	..	..	..	..	..	..	..	..
	Intra-abdominal region	1	1	..	..	..	..	..	..	..	..	..
	Extremities	9	..	..	..	..	..	..	..	..	..	2
Neurogenic fibrosarcoma with tumor giant cells	Intra-abdominal region	1	..	..	..	..	..	..	..	..	..	..
	Extremities	8	1	..	..	..	..	..	..	..	1	..
Total		92	9	1	1	1	2	2	1	1	1	7

preexisting lesions. The experience at the Memorial Hospital, New York, with neurogenic tumors, reported by Stewart,[3] and with fibrosarcoma in general, reported by Quick and Cutler,[4] is not conducive to faith in radiotherapy.

The types of treatment are summarized in table 2. Operation is the most frequent method of treatment and the most successful. In this table amputation has been lumped with other operative procedures. Among the cases of sarcoma of the extremities primary amputation was carried out in four cases and preoperative roentgen radiation in two. Of the four patients, one lived ten years after treatment and died without evidence of the tumor; one is living and well after seven-tenths

3. Stewart, F. W., and Copeland, M. M.: Am. J. Cancer **15**:1235, 1931.
4. Quick, D., and Cutler, M.: Ann. Surg. **86**:810, 1927.

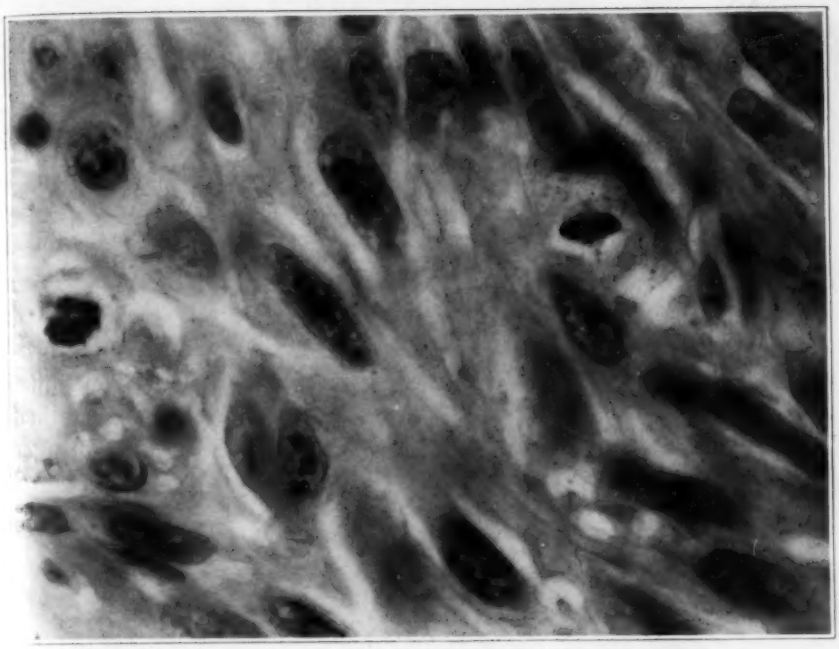

Fig. 2.—Section of fibrosarcoma of the leg, showing collagen and fibroglia rils, mitoses and anaplastic cells. Phosphotungstic acid-hematoxylin stain; 1,160.

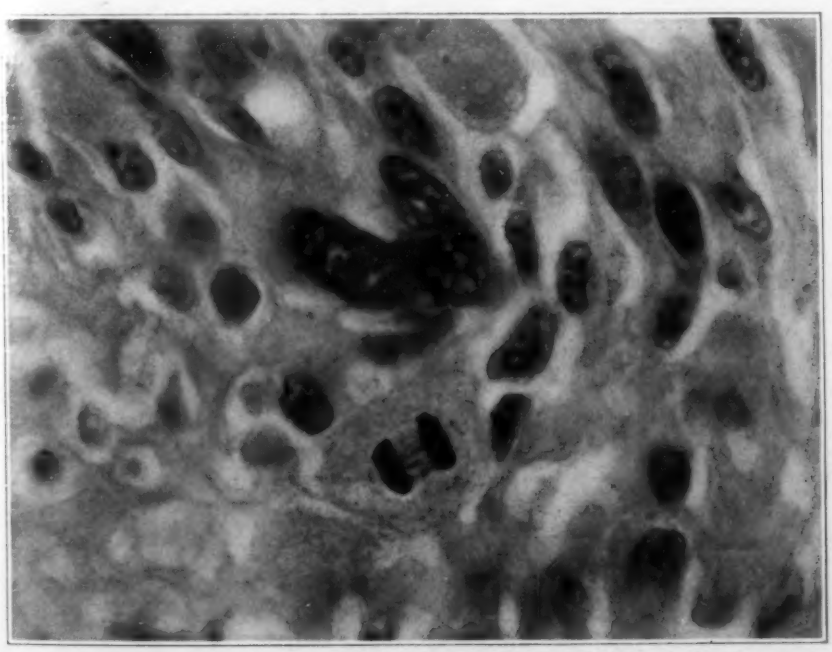

Fig. 3.—Section of fibrosarcoma of the leg, showing little intercellular substance and marked anaplasia. Phosphotungstic acid-hematoxylin stain; × 1,160.

year, and two died with disease at the end of one year. Most of the successful operative procedures have been excision with wide margins, below as well as laterally.

Classification of the fibrosarcomas is a difficult problem and as yet unreliable. We define fibrosarcoma as a tumor of fibroblasts, forming varying amounts of collagen, which is recognized as malignant by its invasive growth, mitotic activity and at times markedly anaplastic character (figs. 2 and 3). Types of tumors ranging from benign fibroma to anaplastic sarcoma exist, and the diagnosis of the more differentiated forms is difficult. While various pathologic subdivisions have been proposed, there are only two which appeal to us as being at present definite. These are the neurogenic fibrosarcoma and a residual type classified simply as fibrosarcoma. In the case of each there are wide ranges of histologic pressure and clinical behavior.

TABLE 3.—*Location of Neurogenic Fibrosarcoma*

Head	8
Trunk	20
Intra-abdominal region	4
Extremities	31
Total	63

We have included as cases of neurogenic fibrosarcoma only those in which we felt that the diagnosis could be made without question. The criteria demanded for this diagnosis have been the arrangement of the cells in definite fascicles with interlacing patterning of the herring-bone type, with a tendency to somewhat wavy, elongate nuclei and with some evidence of palisading of the nuclei (figs. 4 and 5). In cases in which material was available for staining by silver the pericellular distribution of fibrils emphasized by Stout [5] has been of value. There is a tendency to include more cases as instances of neurogenic tumor than is warranted by a critical application of well defined characteristics. We have classified sixty-three cases in this group. The sites of the tumors were widely distributed, but in most cases the growth occurred in the extremities (table 3). In a number it occurred definitely in relation to nerves. In only two cases were the stigmas of neurofibromatosis definitely noted, although they probably existed in others. The useful papers of Stewart and Copeland [3] and Stout [6] should be consulted with regard to this group.

On the basis of our material the distinction between fibrosarcoma that is definitely neurogenic and a growth of less well defined character is largely academic. The significant difference lies between the rapidly progressing fibrosarcoma and the less actively growing tumors.

5. Stout, A. P.: Human Cancer, Philadelphia, Lea & Febiger, 1932.
6. Stout, A. P.: Am. J. Cancer **25**:1, 1935.

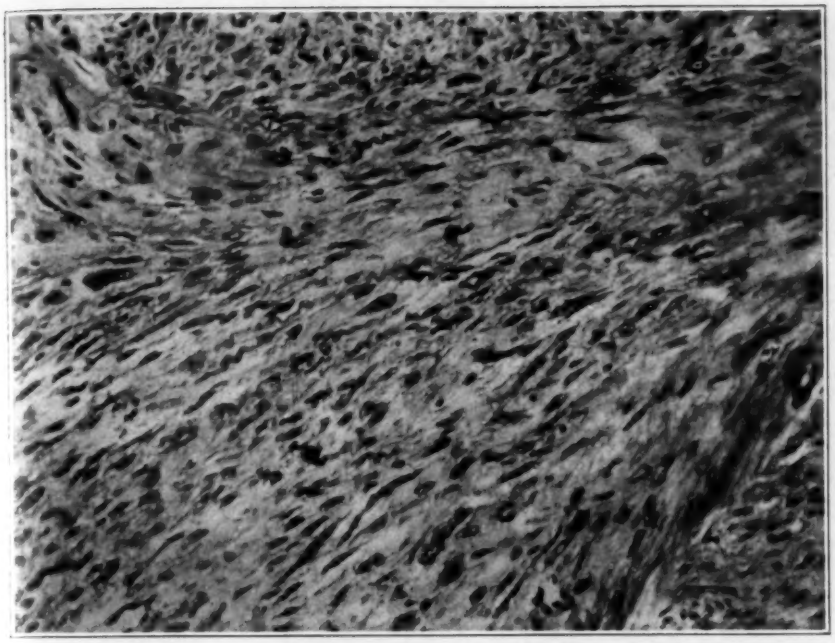

Fig. 4.—Section of neurogenic fibrosarcoma of the leg, showing fascicle formation, elongate nuclei and collagen. Phosphotungstic acid-hematoxylin stain; × 150.

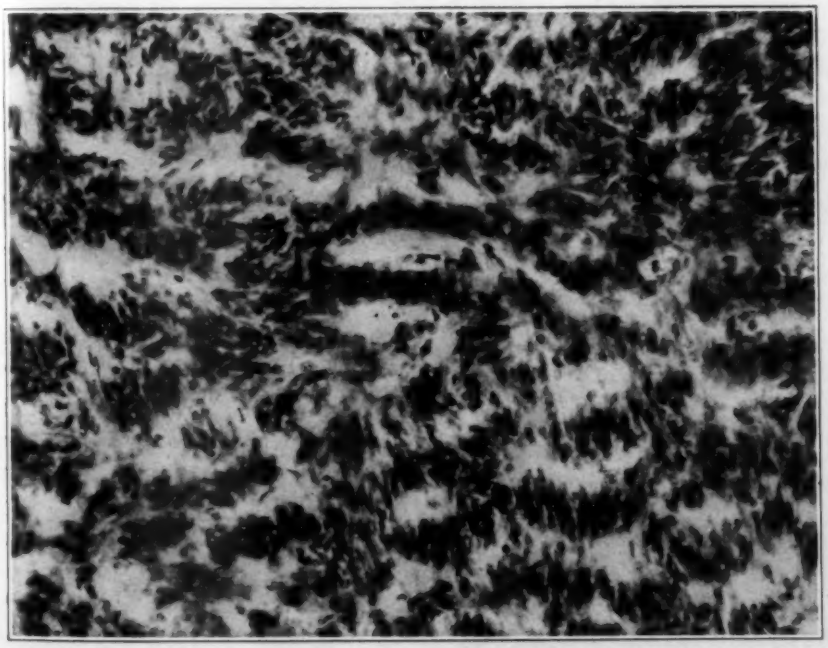

Fig. 5.—Section of neurogenic fibrosarcoma of the skin of the trunk, showing palisading of nuclei. Phosphotungstic acid-hematoxylin stain; × 225.

In our experience the most useful histologic criterion in determining a high degree of malignancy has been the presence of a fair to a marked number of tumor giant cells. By tumor giant cells we mean large cells with two or more nuclei, variable in size and shape, or with large lobulated or bizarre nuclei, rather than unusually large tumor cells with fairly even contours of the nucleus and cytoplasm (fig. 6). Variation in the size of the cell seems to us, as to Stout, of minor significance. The number of tumor giant cells often fairly closely parallels mitotic activity.

However, the neurogenic tumor with tumor giant cells is not strikingly different in behavior from a growth without such cells. In many

Fig. 6.—Section of fibrosarcoma of the leg, showing irregular mitosis and a tumor giant cell. Phosphotungstic acid-hematoxylin stain; × 1,800.

of the cases, particularly in those of neurogenic fibrosarcoma, the growth has shown scattered foci of so-called myxomatous intercellular substance, and several are listed in the tables as definite instances of myxofibrosarcoma. While myxofibrosarcoma may deserve a separate classification, we prefer on the evidence so far available to regard it as a variant of fibrosarcoma, probably owing its appearance to edema of the intercellular substance (fig. 7). Our experience has paralleled that of Stout [6] in our failure to find mucin by specific methods of staining. Only three patients with "myxofibrosarcoma" were encountered in the group. One of these died after three and one-half years, a local operation being

followed by recurrence, which was treated by amputation of the arm, with death occurring from generalized metastases. In the second patient, a woman 45 years of age, the tumor appeared in the right small toe and did not recur after operation. The patient died without disease eight and eight-tenths years after treatment. The third patient is living and well two and five-tenths years after wide excision of a sarcoma of the left lower eyelid.

We have set aside as a separate type the well differentiated desmoid tumor of the abdominal wall, of which five cases were available for

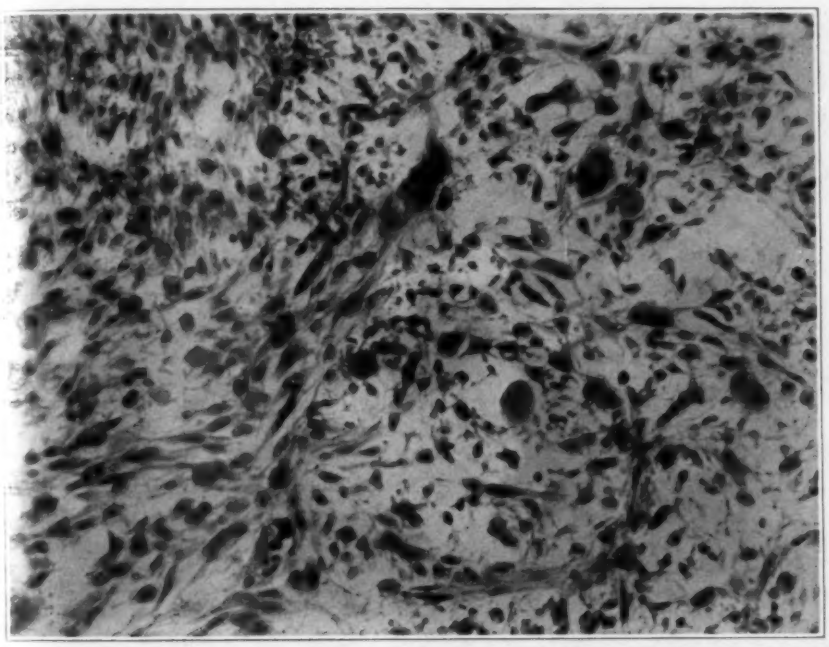

Fig. 7.—Section of fibrosarcoma, showing edema of the stroma (often called myxosarcoma). Phosphotungstic acid-hematoxylin stain; × 200.

study, and also the fibrosarcoma of the breast, of which seventeen cases were found. In most of the latter cases the growth was definitely an adenofibrosarcoma.

In table 4 the cases in which the patient was followed for three years or over, other than those of desmoid tumor and tumor of the breast, are arranged according to histologic classification. The only significant difference here is seen in the low survival rate of the patients with fibrosarcoma with tumor giant cells.

When the average total time of survival of all the patients from the onset of disease is determined, as shown in table 5, the latter group shows a comparatively short course. This checks well with the low

survival rate for this group. Patients with neurogenic fibrosarcoma with tumor giant cells survive a definitely shorter period than those with neurogenic fibrosarcoma without tumor giant cells. The strikingly parallel behavior of fibrosarcoma of the neurogenic type and of fibrosarcoma of the non-neurogenic type is emphasized by those tables, and it suggests that the histologic distinction is without clinical significance save in cases of fibrosarcoma with tumor giant cells.

The total duration in all the cases, grouped according to the end-result, is shown in table 6.

TABLE 4.—*Classification of Fibrosarcoma with Follow Up of Three Years or Over*

	Number of Cases	Alive and Well	Percentage Alive and Well
Fibrosarcoma	43	15	35
Neurogenic fibrosarcoma	38	14	37
Fibrosarcoma with tumor giant cells	26	2	8
Neurogenic fibrosarcoma with tumor giant cells	11	4	36

TABLE 5.—*Average Total Duration from Onset to Death*

Fibrosarcoma	7.0 years
Neurogenic fibrosarcoma	7.8 years
Fibrosarcoma with tumor giant cells	2.2 years
Neurogenic fibrosarcoma with tumor giant cells	5.5 years

TABLE 6.—*Total Duration in All Cases* *

Years	Died	Living with Disease	Living and Well
Under 1	20	0	3
1 to 2	23	1	9
2 to 3	11	0	14
3 to 4	8	0	9
4 to 5	2	1	4
5 to 10	3	2	27
10 to 15	3	0	10
15 to 20	1	0	5
20 to 25	1	1	0
25 to 30	0	1	1
30 to 35	0	0	1
Total	72	6	83

* The duration was unknown in two cases.

Since recurrence developed in over a third of the cases (sixty-four), it is obvious that local removal is often inadequate. In cases with recurrence the prognosis is grave. But eight patients who showed recurrence are living and well after three years. As a rule, if recurrence takes place it occurs within a year. Among the twenty-nine cases in which the time of recurrence was definitely known, in all but two the recurrence took place before a year had passed. The longest interval between the primary operation and recurrence was three years. Thus it can

be stated with a fair degree of probability that if in a given case a year has passed without recurrence there will be no appreciable danger subsequently.

Another feature of importance is the relation of recurrence to metastasis. Among the thirty-four cases with metastasis, in only six did this occur prior to local recurrence, and in two local recurrence was impossible because amputation had been done as the first operation. One must then recognize recurrence as having grave prognostic significance, not only with regard to the likelihood of metastasis but with regard to an ultimate fatal outcome of the disease. For this reason adequate removal at the first operation is of prime importance. In cases in which the lesion in an extremity has reached such a size that an adequate margin of healthy tissue cannot be excised with it, amputation is definitely indicated. In the past it has been our usage to recommend conservative treatment of small lesions, risking one recurrence and resorting to amputation if this recurrence appeared. In the light of the present findings, however, it would seem that this procedure is too hazardous and that extensive local removal or amputation should be resorted to at once.

Metastasis occurred in only one fifth of the cases. The lungs were the most frequently involved of the viscera. Metastasis of sarcoma to lymph nodes is not generally expected, yet it does occur. Willis [7] did not record any instances of metastasis of fibrosarcoma to lymph nodes. Stewart and Copeland [3] mentioned that it occurs but stated: "Dissemination to node areas is by way of venous emboli." Figure 8 shows metastasis to a lymph node. We have encountered other instances in cases not included in this study.

The location of the tumor may be of more importance than its histologic type. We have therefore presented our cases in relation to the point of origin, grouping those of tumor of the head, trunk, abdominal wall, breast, intra-abdominal region and extremities. This classification is particularly useful from the clinical standpoint.

When this division is made tumor of the head or face stands out as of particularly high malignancy, difficult to treat (table 7). There were twenty-four patients with such a growth, with an average age of 55.8 years; 58 per cent were males and 42 per cent females. The average duration of the disease was six and six-tenths years. The mortality was high in this group. Eight patients, or 33 per cent, are alive without recurrence, and only 21 per cent are living without disease after three years or more. Two additional patients are living with disease, one twenty-nine years after the onset, with eight recurrences through that period. One was a woman with a neurogenic fibrosarcoma

7. Willis, R. A.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, Ltd., 1934.

TABLE 7.—*Fibrosarcoma of the Head*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Results: Alive and Well, Years	Results: Living With Disease	Results: Died Without Disease	Results: Died With Disease	Pathologic Diagnosis
1	53	♀	?	Large	Nasopharynx	Operation	8	0	29.0	29.0	....	+	..	..	Neurogenic fibrosarcoma
2	60	♂	6	Small	Under chin	Operation	0	0	15.0	15.5	15.0	..	..	..	Neurogenic fibrosarcoma
3	60	♂	?	Large	Nasopharynx	Operation	Several	0	1.1	1.2	....	..	..	+	Fibrosarcoma
4	61	♂	24	?	Parotid	Operation	0	0	12.5	14.5	12.5	..	..	..	Neurogenic fibrosarcoma
5	31	♂	3	Small	Tooth socket	None	0	0	....	2.5	....	..	..	+	Fibrosarcoma with tumor giant cells
6	58	♀	26	Large	Upper part of cheek	Operation	2	0	0.8	3.0	....	..	..	+	Neurogenic fibrosarcoma associated with the second division of the fifth nerve
7	60	♀	48	Large	Scalp	Radium; roentgen rays	0*	0	1.5	5.5	....	..	..	+	Fibrosarcoma
8	59	♀	?	Large	Nasopharynx	Operation	3	0	0.8	0.8	....	..	..	+	Fibrosarcoma with tumor giant cells
9	63	♂	60	Large	Upper lip	Roentgen rays; radium	6	0	6.0	11.0	....	..	..	+	Fibrosarcoma
10	72	♀	5	Small	Right brow	Operation	0	0	0.7	1.1	....	..	+	..	Fibrosarcoma with tumor giant cells
11	?	♂	24	Small	Lower middle gum	Operation	0	0	7.5	9.5	7.5	..	..	..	Fibrosarcoma
12	20	♂	2	Large	Gum	Radium	0*	0	0.3	0.4	....	..	..	+	Fibrosarcoma with tumor giant cells
13	49	♂	3	Large	Mouth	None	0	0	...	0.3	....	..	..	+	Fibrosarcoma
14	48	♂	192	Large	Nasopharynx	Operation	2	0	6.5	23.0	....	+	..	..	Fibrosarcoma, also epidermoid carcinoma, grade I
15	72	♂	12	Small	Tongue	Operation	1	+	0.7	1.7	....	..	..	+	Neurogenic fibrosarcoma
16	33	♂	?	Large	Jaw	Operation	4	0	9.0	9.0	5.0	..	..	..	Fibrosarcoma
17	54	♂	?	Small	Right lid	Radium	5	+	8.5	8.5	....	..	..	+	Fibrosarcoma; this may be fibrosarcoma arising after irradiation; section from recurrent growth
18	43	♀	?	Small	Forehead	Operation	2	0	3.0	3.0	0.3	..	..	..	Fibrosarcoma
19	48	♀	1	Small	Mouth	Operation; roentgen rays	0	+	1.5	1.6	....	..	..	+	Fibrosarcoma with tumor giant cells
20	61	♀	1	Small	Upper jaw	Operation	3	0	0.8	0.9	....	..	..	+	Fibrosarcoma with tumor giant cells
21	64	♀	5	Small	Upper part of cheek	Operation	2	0	1.2	1.6	....	..	..	+	Neurogenic fibrosarcoma associated with the second division of the fifth nerve
22	78	♂	36	Small	Left lower lid	Operation	0	0	2.1	5.1	2.5	..	..	..	Myxofibrosarcoma
23	60	♂	36	Large	Upper part of cheek	Operation	2	0	5.5	8.5	3.0	..	..	..	Neurogenic fibrosarcoma
24	77	♀	8	Small	Face	Operation	0	0	0.8	1.5	0.8	..	..	..	Neurogenic fibrosarcoma with tumor giant cells

* Persistence.

originating in the nasopharynx, who was 37 years of age when the disease first appeared. Half the tumors were noted as definitely small when first seen. The other half were fairly extensive. Four patients were treated primarily by irradiation, although operation was resorted

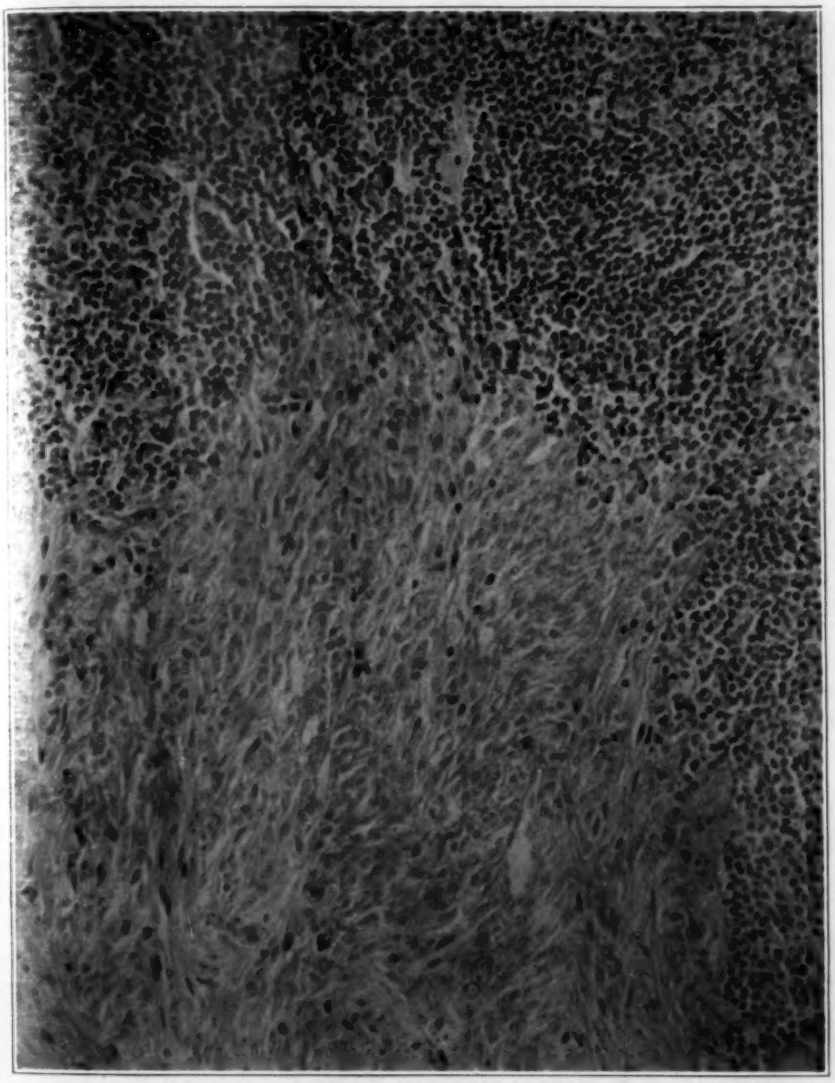

Fig. 8.—Section of fibrosarcoma metastatic to a lymph node. Hematoxylin-eosin stain; × 120.

to for recurrence in two of these cases. All these patients who were treated by irradiation died with disease. In all but two of the cases in which recurrent tumors were treated roentgen therapy or radium was

* Persistence.

utilized. One patient lived for eleven years and finally died with disease, having had two recurrences. One case is of particular interest in that there was a five year cure after four recurrences. Thirteen patients, or more than half, showed recurrence. In eight of these recurrence took place less than a year after the first treatment; in the case of four the time was unknown, and in one the recurrence was seven years after treatment of the primary tumor. As there was no biopsy of the initial tumor in the last-mentioned case, it is possible that it might be a fibrosarcoma that developed at the site of an irradiated cutaneous cancer of the face, although the assumption is that the earlier tumor was also a fibrosarcoma.

Only three patients showed metastasis, one to lymph nodes and one to the parotid gland and submaxillary nodes; the third showed generalized metastases. One instance of multiple tumor occurred in this group; in case 14 the neoplasm was an epidermoid carcinoma, of grade 1, of the oral mucosa, that developed adjacent to the fibrosarcoma of the nasopharynx. One probable myxosarcoma was found.

In eight of the cases the tumor was readily distinguished as a neurogenic fibrosarcoma on histologic examination. The average duration in these cases was nine and five-tenths years, or half again as long as that in the entire series of cases of fibrosarcoma of the head. In two cases the tumor was definitely associated with the second division of the fifth nerve, one growth ultimately extending along the course of the nerve to the gasserian ganglion.

The average duration in the cases of non-neurogenic tumor in this group was only four and two-tenths years. Here, then, is a distinct correlation between the length of life after the onset of disease and the histologic appearance of the tumor, the patients with well differentiated neurogenic fibrosarcoma showing an average duration twice as long as the group of those with fibrosarcoma and ten times as long as those with sarcoma with tumor giant cells. If one were to exclude from the instances of neurogenic tumor cases of fibrosarcoma showing tumor giant cells, the average duration would be even longer.

The malignancy in the cases of sarcoma with tumor giant cells is definitely much higher than that in the group as a whole, the seven patients with this type of tumor showing a total duration of the disease of only nine-tenths year after the onset.

Of the thirteen patients with fibrosarcoma of the head with recurrences, one patient had eight recurrences, one had six, one had five, one had four, two had three, five had two, one had "several" and one had one. Of the patients who had recurrences, three are living without disease, one five years and two less than a year after the onset. Two patients showed persistence of the tumor in spite of treatment.

Our largest group and perhaps the one of greatest practical importance to the surgeon is the cases of sarcoma of the extremities (table 8). There were sixty-two patients with an average age of 49.1 years; 52 per cent were males. The average duration of the disease was five and two-tenths years. The youngest patient, a male, showed a tumor of the right hand at birth. Excision was followed by twenty recurrences; the patient was treated by fourteen operations, considerable radium irradiation and finally amputation. He died with disease at the age of 16, of paralysis resulting from involvement of the spinal cord in the tumor. The next youngest patient, a girl of 7 months, is living and well thirteen years after operation. Fourteen patients, or 24 per cent, are living and well more than three years after the onset. None of these patients has had any recurrence. Thirty-two of the sixty-two patients, or over half, had recurrences, the number ranging from one to more than twenty.

Twenty-three patients in this group showed the presence of tumor giant cells on histologic examination. Of these, only five are living and well after three years, and for the eighteen who died the average total duration of the disease was only one and three-tenths years. This parallels the high malignancy of this form of tumor in other parts of the body.

In this group there were three instances of multiple tumor. One case, that of a 45 year old woman, is particularly interesting in that the metastases to the inguinal region were the first to attract attention, and only at the second operation was the primary tumor on the right small toe discovered and removed. The patient remained without evidence of the sarcoma for three and one-half years after operation but died of an extensive colloid carcinoma of the stomach after six operations for metastases.

The second case of multiple tumor occurred in a 29 year old woman with a neurogenic fibrosarcoma of the lower part of the leg and a carcinoma of the rectum, who died as a result of the carcinoma of the rectum three and five-tenths years after the operation for the neurogenic fibrosarcoma.

The third patient, an elderly woman, died with extensive fibrosarcoma of the left thigh and carcinoma simplex of the same location, presumably a metastatic lesion.

In an effort to determine what the influence of age might be, the patients over 65 years of age were selected. Of these, eight died with disease; three are living with disease, and only three are living and well after nine and eight-tenths years, one and seven-tenths years and seven-tenths years, respectively. Thus age is not a factor.

TABLE 8.—*Fibrosarcoma of the Extremities*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Results: Alive and Well, Years	Results: Living With Disease	Results: Died Without Disease, Yrs.	Results: Died With Disease	Pathologic Diagnosis
1	41	♀	180	Small	Lower part of left leg	Operation	0	0	14.0	21.0	14.0	..	..	..	Fibrosarcoma
2	64	♀	?	Small	Upper part of arm	Amputation	0	0	10.8	10.8	....	..	10.8	..	Fibrosorcoma
3	?	♂	24	Small	Over tendon of quadriceps at left knee	Operation	0	0	13.0	15.0	13.0	..	..	..	Fibrosarcoma
4	0.7	♀	3	Small	Upper part of arm	Operation	0	0	12.7	13.0	12.7	..	..	..	Fibrosarcoma
5	59	♀	24	Small	Right deltoid region	Operation	0	0	12.0	14.0	12.0	..	..	..	Fibrosarcoma
6	13	♂	12	Small	Right forearm	Operation	0	0	10.7	11.7	10.7	..	.	..	Fibrosarcoma
7	30	♂	10	Large	Below elbow	Amputation	0	+	1 0	1.8	...	.	..	+	Fibrosarcoma
8	76	♂	36	Small	Right thigh	Operation	0	0	9.7	12.7	9.7	..	..	..	Neurogenic fibrosarcoma with tumor giant cells
9	61	♀	30	Large*	Arm	Operation	1	+	1.0	3.5	...	..	..	+	Myxofibrosarcoma with tumor giant cells
10	30	♀	3	Small	Left thigh	Operation †	8	0	3 0	3.2	..	..	..	+	Fibrosarcoma with tumor giant cells
11	36	♂	4	Small	Right groin	Operation †	0‡	0	0.2	0.5	...	..	..	+	Fibrosarcoma
12	0	♂	?	Small	Right hand	Operation	20	+	?	16.0	...	..	..	+	Fibrosarcoma
13	45	♀	20	Small	Right small toe	Operation	0	+	8.8	10.5	...	..	8.8	..	Myxofibrcsarcoma
14	60	♀	12	Small	Right calf	Operation; roentgen rays	0	0	9.7	10.7	9.7	..	..	..	Neurogenic fibrosarcoma with tumor giant cells
15	81	♀	10	Small	Left thigh	Operation	2	+	0.5	1.3	...	..	..	+	Fibrosarcoma
16	53	♂	4	Large	Lower part of right leg	Operation	4	0	0.7	1.0	. .	..	..	+	Fibrosarcoma
17	45	♂	1	Small	Right forearm	Operation; roentgen rays	0	0	8.5	8.6	8.5	..	..	..	Fibrosarcoma
18	37	♀	120	Small	Leg	Operation	0	0	8.2	18 2	8.2	..	..	..	Neurogenic fibrosarcoma with tumor giant cells
19	45	♂	12	Small	Left thigh	Operation	4	0	8.0	9.0	0.1	..	..	..	Neurogenic fibrosarcoma
20	51	♀	?	Small	Right thigh	Operation	0	0	7.8	7.8	7.8	..	..	..	Fibrosarcoma
21	70	♂	8	Large	Calf	Operation	1	0	0.2	0.9	...	..	..	+	Neurogenic fibrosarcoma
22	55	♂	2	Small	Right thigh	Operation	6	0	7.7	7.9	0.1	..	..	..	Fibrosarcoma
23	48	♂	18	Large	Right forearm	Amputation	0	+	1.0	2.5	...	..	..	+	Fibrosarcoma
24	29	♀	?	Small	Lower part of right leg	Operation	0	0	3.5	3.5	...	..	3.5	..	Neurogenic fibrosarcoma
25	71	♂	2	Large	Right thigh	Operation	1	0	0.9	1.1	...	..	0.9	..	Neurogenic fibrosarcoma
26	67	♀	3	Large	Right thigh	Operation	1	0	0.7	0.9	...	..	..	+	Fibrosarcoma
27	76	♀	18	Large	Upper part of leg	Operation	2	+	1.5	2.9	...	..	..	+	Fibrosarcoma with tumor giant cells

TABLE 8.—*Fibrosarcoma of the Extremities—Continued*

TABLE 8.—*Fibrosarcoma of the Extremities—Continued*

28	49	♂	4	Large	Left forearm	Operation	1	+	2.0	4.0	...	..	..	+	Fibrosarcoma with tumor giant cells
29	?	♂	24	Large	Left thigh	Operation	1	+	2.0	4.0	...	..	..	+	Fibrosarcoma with tumor giant cells
30	30	♂	144	Small	Over left deltoid	Operation	0	0	6.2	18.2	6.2	..	..	..	Neurogenic fibrosarcoma
31	55	♀	3	Small	Right thigh	Operation	1	0	5.3	5.5	5.0	..	..	..	Neurogenic fibrosarcoma with tumor giant cells
32	32	♂	4	Large	Right hand	Radium; operation	0‡	+	1.4	1.7	...	..	..	+	Neurogenic fibrosarcoma with tumor giant cells
33	34	♂	?	Small	Foot	Operation	1	+	3.0	3.0	...	..	..	+	Neurogenic fibrosarcoma
34	66	♂	?	Small	Thigh	Operation	1	0	0.7	0.7	...	..	..	+	Neurogenic fibrosarcoma
35	22	♀	72	Small	Above left knee	Operation	2	0	8.0	14.0	1.7	..	..	..	Neurogenic fibrosarcoma
36	52	♀	?	Small	Right hand	Operation	1	0	5.2	5.2	5.0	..	..	..	Fibrosarcoma
37	?	♀	12	Large	Left thigh	None	0	0	...	1.0	...	..	..	+	Fibrosarcoma with tumor giant cells
38	71	♂	12	Small	Right heel	Operation	1	+	1.1	2.1	...	..	..	+	Fibrosarcoma with tumor giant cells
39	29	♂	26	Small	Left groin	Operation	3	0	4.7	6.9	0.3	..	..	..	Neurogenic fibrosarcoma
40	46	♂	36	Large	Right knee	Operation	0	0	3.0	6.0	3.0	..	..	..	Fibrosarcoma with tumor giant cells
41	60	♂	3	Small	Right thigh	Operation	5	0	4.6	4.8	0.1	..	..	..	Neurogenic fibrosarcoma with tumor giant cells
42	58	♀	5	?	Right thigh	Operation	1	+	1.1	1.5	...	..	..	+	Neurogenic fibrosarcoma with tumor giant cells
43	?	♀	3	Large	Right thigh	Operation	1	+	1.0	1.2	...	..	..	+	Fibrosarcoma with tumor giant cells
44	50	♀	4	Small	Upper part of left arm	Operation	0	0	1.8	2.1	1.8	..	..	..	Neurogenic fibrosarcoma
45	64	♂	18	Small	Groin	Operation; roentgen rays	0	0	0.7	2.2	0.7	..	..	..	Neurogenic fibrosarcoma
46	43	♂	5	Large	Left leg	Operation	1	+	1.9	1.3	...	..	..	+	Neurogenic fibrosarcoma with tumor giant cells
47	70	♂	4	Small	Lower part of right leg	Operation	1	+	0.5	0.8	...	..	..	+	Fibrosarcoma with tumor giant cells
48	14	♀	4	Small	Right knee	Operation	2	0	1.8	2.1	1.3	..	..	..	Neurogenic fibrosarcoma with tumor giant cells
49	21	♀	72	Small	Sole of foot	Operation	2	0	2.0	8.0	1.7	..	..	..	Neurogenic fibrosarcoma
50	50	♀	?	Small	Thigh	Operation	0	0	2.0	2.0	2.0	..	..	..	Neurogenic fibrosarcoma
51	70	♀	60	Small	Lower part of left leg	Operation	0	0	1.7	6.7	1.7	..	..	..	Neurogenic fibrosarcoma
52	47	♀	4	Large	Right thigh	Roentgen rays; operation	0‡	+	1.5	1.8	...	..	..	+	Neurogenic fibrosarcoma; Recklinghausen's disease
53	76	♀	?	Large	Calf	Operation	1	+	1.3	1.3	...	+	..	..	Neurogenic fibrosarcoma
54	53	♀	3	Small	Over left deltoid region	Operation	0	0	2.7	2.9	2.7	..	..	..	Fibrosarcoma
55	29	♂	5	Large	Right thigh	Operation	1	+	1.2	1.6	...	..	..	+	Neurogenic fibrosarcoma with tumor giant cells
56	42	♀	7	Small	Upper part of left arm	Operation	2	0	1.8	2.4	0.7	..	..	..	Neurogenic fibrosarcoma
57	84	♀	0.5	Large	Leg	None	0‡	0	...	0.1	...	..	..	+	Fibrosarcoma with tumor giant cells
58	38	♂	24	Large	Arm	Roentgen rays; amputation	0	0	0.7	2.7	0.7	..	..	..	Fibrosarcoma with tumor giant cells
59	67	♂	2	Small	Toe; sole	Operation	1	0	0.7	0.9	0.7	..	..	..	Neurogenic fibrosarcoma
60	75	♂	24	Small	Right knee	Operation	0	0	0.2	2.2	...	..	0.2	..	Neurogenic fibrosarcoma
61	65	♂	24	Small	Left thigh	Operation	4	0	1.4	3.4	0	..	..	..	Neurogenic fibrosarcoma with tumor giant cells; Recklinghausen's disease
62	23	♂	48	Small	Elbow	Operation	0	0	3.2	7.2	3.2	..	..	..	Neurogenic fibrosarcoma

* Multiple tumors. † Erysipelas and prodigiosus toxins. ‡ Persistence.

Thirty-one patients with neurogenic fibrosarcoma in this group showed no significant difference in total duration from the group as a whole, the figures for this group being four and seven-tenths years, as against four and nine-tenths years.

We encountered thirty-eight cases of sarcoma of the trunk exclusive of the tumor of the breast and of desmoid tumor of the abdominal wall (table 9). In approximately all the cases the tumor was of subcutaneous origin. The average age of the thirty-eight patients was 46.7 years; 63 per cent were males and 37 per cent females. The average duration of disease from the onset to death or the end of the follow up was four and eight-tenths years. Recurrence developed in fourteen cases, in eight in less than a year and in two additional cases in less than two years; in four cases the exact time of recurrence is unknown. Thus it will be seen that the time of recurrence corresponds closely with that in the cases of fibrosarcoma elsewhere and that a fair prognosis can be given for those patients who have lived one year without evidence of recurrent disease.

The danger of metastasis is apparently considerably over-rated here, as in the cases of fibrosarcoma of the extremities, as metastasis occurred in only six of the group, or 17 per cent. There is no significant difference between the behavior of the neurogenic sarcoma and the other types of fibrosarcoma so far as metastasis is concerned. One case (21), that of a 56 year old man in whom the tumor was primary in the anterior wall of the chest, is of particular interest in that the growth involved the axillary nodes. The extensive metastasis appeared only after a local recurrence. This patient is alive and well three and eight-tenths years after operative removal of the recurrent growth and the metastasis.

In nineteen cases the tumor could be recognized histologically as of neurogenic type, and the average total duration was of seven years. Fourteen patients are alive and well; seven, or 30 per cent, showed recurrence after more than three years; this is practically the same proportion as for the entire group, fourteen of thirty-seven. In some of the cases the tumor undoubtedly would not have recurred were it not for the inaccessibility of the lesion, which rendered complete operative removal extraordinarily difficult. Thus, in case 22, that of a man 37 years of age who had a small neurogenic fibrosarcoma of the upper part of the chest, apparently arising from an intercostal nerve, there were four recurrences over a period of five years, and the patient is living and well two months after the last operation, although it is probable that there may be another recurrence.

An illustration of the favorable outcome in a case of neurogenic fibrosarcoma, even when the tumor is extensive, is shown in case 36, that of a 26 year old man who had a neurogenic fibrosarcoma involving

the brachial plexus above and below the clavicle, which was very extensive when first seen, two years after symptoms were noted. Amputation of the shoulder girdle was done, and there has since been no recurrence or evidence of metastasis. The patient is living and well five and two-tenths years after the operation. Interestingly, this patient had coexistent active tuberculosis of the axillary nodes, and in the specimen removed at operation an intimate intermingling of the tuberculous process and the tumor was noted. Of the ten patients in this group who are living and well more than three years after the onset, four had recurrences (one patient had four, two had two, and one had one).

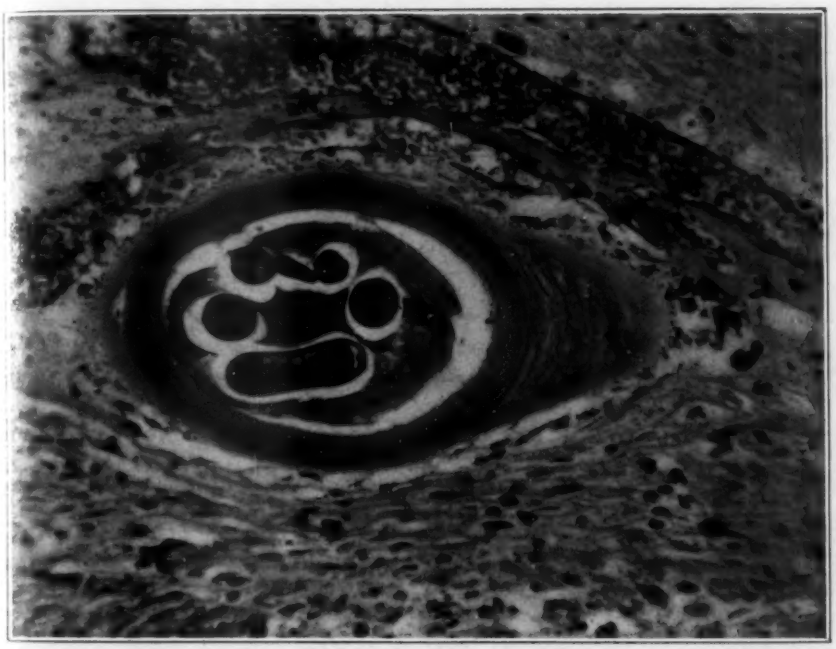

Fig. 9.—Section of fibrosarcoma of the shoulder, containing an encysted trichinella. Hematoxylin-eosin stain; × 200.

All these were treated by operation, only one receiving roentgen treatment in addition to the operative procedure. The long duration in some of the cases is of striking interest; thus, in case 38, a man 42 years of age had a tumor of the right lower quadrant of the abdomen for fifteen years, which was treated by operation; four recurrent growths which were treated by both operation and the roentgen rays, and final metastasis to the lung after a total duration of twenty years.

The sarcoma with tumor giant cells maintained the same high level of malignancy as in other localities. There were eight cases of this type of growth, and only two patients are living and well, one after two and eight-tenths years, the other after six years. The average

TABLE 9.—*Fibrosarcoma of the Trunk*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Results: Alive and Well, Years	Results: Living With Disease	Results: Died Without Disease, Yrs.	Results: Died With Disease	Pathologic Diagnosis
1	43	♀	1	Small	Left scapular region	Operation	1	+	0.4	0.5	....	..	..	+	Fibrosarcoma with tumor giant cells; also Trichinae in the tumor
2	37	♀	3	Large	Right gluteal region	Operation; incomplete	0‡	0	0.1	0.3	....	..	..	+	Fibrosarcoma with tumor giant cells; also adenocarcinoma of the uterus
3	13	♂	?	Small	Shoulder	Operation	0	0	12.7	12.7	12.7	..	..	..	Neurogenic fibrosarcoma
4	42	♀	6	?	Right scapular region	Operation	0	0	2.0	2.5	....	..	2.0	..	Neurogenic fibrosarcoma
5	63	♂	24	Small	Lumbar region	Operation; roentgen rays	0	0	1.2	3.2	....	..	1.2	..	Neurogenic fibrosarcoma
6	33	♀	?	?	Neck	Operation	4	0	31.0	31.0	9.0	..	..	..	Neurogenic fibrosarcoma
7	49	♂	36	Small	Posterior part of axilla	Operation	0	0	10.0	13.0	10.0	..	..	..	Neurogenic fibrosarcoma
8	55	♂	6	Small	Left lumbar region	Operation	0	0	2.5	3.0	....	..	..	+	Fibrosarcoma with tumor giant cells
9	50	♂	?	?	Right shoulder	Operation	1	0	8.2	8.2	8.2	..	..	..	Neurogenic fibrosarcoma
10	48	♂	24	Small	Right scapular region	Operation; roentgen rays	1	0	7.7	9.7	2.7	..	..	..	Neurogenic fibrosarcoma
11	53	♂	2	Large	Anterior wall of chest	Operation; roentgen rays	0‡	0	0.5	0.7	...	..	..	+	Fibrosarcoma
12	43	♀	12	Large	Shoulder	Operation; roentgen rays; radium	2	0	1.2	2 2	...	..	..	+	Fibrosarcoma
13	37	♀	?	Large	Upper part of back	None	0	+	...	1.2 (?)	..	..	..	+	Neurogenic fibrosarcoma
14	60	♂	12	Large	Right buttock	Operation; roentgen rays	0	0	6.0	7.0	6.0	..	..	..	Fibrosarcoma with tumor giant cells
15	48	♂	60	?	Left shoulder	Operation	2	0	11.0	16.0	5.2	..	..	..	Neurogenic fibrosarcoma
16	61	♂	12	Small	Neck	Operation	2	+	1.0	2.0	...	.	..	+	Fibrosarcoma with tumor giant cells
17	?	♂	?	Large	Back	Operation	0	0	5.3	5.3	5.3	..	..	..	Neurogenic fibrosarcoma
18	55	♂	12	Small(?)	Side	Operation	0	0	1.5	2.5	...	..	1.5	..	Neurogenic fibrosarcoma
19	?	♂	?	Small	Chest	Operation	1	0	5.5	5.5	...	+	..	..	Fibrosarcoma
20	26	♀	24	Small	Over sacrum	Operation	4	+	2.5	4.5	...	..	..	+	Fibrosarcoma
21	56	♂	5	Small	Over left breast	Operation	2	+	4.0	4.4	3.8	..	..	..	Fibrosarcoma with tumor giant cells
22	37	♂	2	Small	Upper part of right side of chest	Operation	4	0	4.8	5.0	0.2	..	..	..	Neurogenic fibrosarcoma
23	70	♀	?	?	Above left clavicle	Operation	2	+	1.0	1.0	...	..	..	+	Neurogenic fibrosarcoma
24	27	♂	4	Small	Below left ear	Operation; radium	0	0	1.2	1.5	1.2	..	..	..	Neurogenic fibrosarcoma
25	54	♂	?	Small	Right groin	Operation	5	0	3.2	3.2	0.2	..	..	..	Neurogenic fibrosarcoma
26	55	♂	Years	Small	Neck	Operation	0	0	1.8	1.8+	1.8	..	..	..	Fibrosarcoma
27	35	♀	12	Small	Over scapula	Operation	0	0	1.8	2.8	1.8	..	..	..	Neurogenic fibrosarcoma
28	31	♀	1	Small	Over left breast	Operation	0	0	1.7	1.8	1.7	..	..	..	Neurogenic fibrosarcoma
29	81	♂	24	Large	Right buttock	Operation	0	0	0.5	2.5	...	..	0.5	..	Fibrosarcoma with tumor giant cells
30	52	♂	72	Large	Shoulder	Operation	0	0	0.5	6.5	0.5	..	..	..	Neurogenic fibrosarcoma
31	37	♀	36	Small	Left buttock	Operation	0	0	0.3	3.3	0.3	..	..	..	Neurogenic fibrosarcoma
32	54	♀	?	Large	Pectoral fascia	Operation	1	0	1.0	1.0	...	..	..	+	Fibrosarcoma with tumor giant cells
33	41	♀	?	Small	Labia	Operation	0	0	6.5	6.5	6.5	..	..	..	Fibrosarcoma
34	50	♀	1	Small	Axilla	Operation	0	0	0.5	1.5	0.5	..	..	..	Fibrosarcoma
35	?	♂	?	Small	Neck	Operation	0	0	1.9	1.9	1.9	..	..	..	Fibrosarcoma
36	26	♂	24	Large	Brachial plexus	Operation; amputation of shoulder girdle	0	0	5.2	7.2	5.2	..	..	..	Neurogenic fibrosarcoma; also tuberculosis of lymph nodes
37	72	♂	?	?	Back	Operation; roentgen rays	0	0	0.3	0.3	...	..	0.3	..	Myxofibrosarcoma with tumor giant cells
38	42	♂	204	Small	Abdominal wall, right lower quadrant	Operation	4	+	3.7	20.0	...	..	..	+	Fibrosarcoma

duration in the fatal cases was one and five-tenths years, as against four and three-tenths years for all tumors that were primary in the trunk.

A curious finding in one of the cases of fibrosarcoma with tumor giant cells, in which the growth developed in a 43 year old woman in the left scapular region, was extensive invasion of the fibrosarcoma with trichinas (fig. 9). Whether this was an actual invasion of the tumor by trichinas or whether it was caused by destruction of muscle in which the encysted organisms lay and subsequent inclusion in the growth of the tumor, it is impossible to say. We have observed trichinas in two other cases of malignant disease, one a case of osteogenic sarcoma of the humerus and the other a case of epidermoid carcinoma with extensive involvement of muscle.

One striking group is the cases of tumors within the abdomen and of the genitalia (table 10). The cases of undifferentiated retroperitoneal tumor are not included, only those in which the tumor grew definitely as fibrosarcoma being listed. There are twelve cases in the group, with an average age for the patients of 47.7 years and an average duration of the disease of two and seven-tenths years. One third of the patients were males. Two patients are living and well after three and eight-tenths years and six and six-tenths years, respectively; eight died with disease, and two are living with disease. The tumors in the latter cases are of interest, one because of extreme malignancy on histologic examination and rapid initial development, the other because of neural origin and very well differentiated structure, the growth being a fairly defined neurogenic fibrosarcoma. In one case (2) the first tumor developed in a 43 year old man and was primary in the prostate. Tumor giant cells, great mitotic activity and very poor differentiation pointed to a rapidly growing tumor. Recurrence took place within a month after the initial operation, but with the aid of repeated roentgen treatment the tumor has been held in check, and the patient has been living with disease, working most of the time, for seven and one-half years. When seen recently he had stopped work temporarily for a course of irradiation; a large pelvic mass was present. In contrast to this case is case 12, that of a 50 year old woman who had an extensive but well differentiated neurogenic fibrosarcoma involving the pelvic structures, who came for treatment three months after the development of symptoms; the tumor presented in the groin by extension through the obturator foramen. Incomplete operative removal aided by radium and the roentgen rays has held the tumor in check for a period of four and three-tenths years.

The desmoid tumor of the abdominal wall (table 11) constitutes a distinct type. In practically all cases such a growth arises from the region of the sheath of the rectus muscle. It occurs in relatively young

TABLE 10.—*Intra-Abdominal Fibrosarcoma*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Results				Pathologic Diagnosis
											Alive and Well, Years	Living With Disease, Years	Died Without Disease	Died With Disease	
1	44	♀	9	Small	Abdomen	Operation	0*	0	0.2	0.9	....	..	..	+	Myxosarcoma with tumor giant cells
2	43	♂	1	Large	Prostate	Operation; roentgen rays	1	+	7.5	7.6	....	7.5	..	..	Fibrosarcoma with tumor giant cells
3	40	♂	?	Large	Mesentery	Operation; roentgen rays	1	0	1.2	1.2	....	..	..	+	Fibrosarcoma
4	49	♀	12	Large	Abdomen	Operation	1	+	1.8	2.8	....	..	..	+	Fibrosarcoma
5	54	♀	12	Large	Abdomen	Operation	0	+	1.0	2.0	....	..	..	+	Myxosarcoma
6	38	♂	6	Large	Mesentery	None	0	0	...	0.5	....	..	..	+	Neurogenic fibrosarcoma
7	42	♀	?	Large	Retroperitoneal region	Operation	0	0	3.8	3.8	3.8	..	..	..	Neurogenic fibrosarcoma
8	51	♀	4	Large	Retroperitoneal region	Operation	0	0	0.1	0.4	....	..	..	+	Neurogenic fibrosarcoma with tumor giant cells
9	56	♀	?	Small	Vagina	Palliative	0*	0	?	1.0	....	..	..	+	Fibrosarcoma; also epidermoid carcinoma, grade I, of the anus
10	64	♂	12	Large	Prostate	Operation; roentgen rays	0	0	0.8	1.8	....	..	..	+	Fibrosarcoma
11	41	♀	?	Large	Labium	Operation	0	?	6.5	6.5	6.5	..	..	..	Fibrosarcoma
12	50	♀	3	Large	Pelvis and groin	Operation; roentgen rays; radium	0*	0	4.3	4.5	....	4.3	..	..	Neurogenic fibrosarcoma

* Persistence.

TABLE 11.—*Desmoid Tumors of the Abdominal Wall*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Results				Pathologic Diagnosis
											Alive and Well, Years	Living With Disease	Died Without Disease	Died With Disease	
1	31	♂	6	Small	.....	Operation; roentgen rays	0	0	2.1	2.6	2.2	..	..	..	Fibrosarcoma, desmoid type
2	25	♀	2.5	Small	.....	Operation	0	0	2.5	2.7	2.5	..	..	..	Fibrosarcoma, desmoid type; multiple growth: three malignant adenomas of the colon
3	53	♀	?	Small	.....	Operation	0	0	5.2	5.2	5.2	..	..	..	Fibrosarcoma, desmoid type
4	52	♂	?	Small	.....	Operation	0	0	4.5	4.5	4.5	..	..	..	Fibrosarcoma, desmoid type
5	29	♀	12	Large	.....	Operation	0	0	1.5	2.5	1.5	..	..	..	Fibrosarcoma, desmoid type

adults and responds uniformly well to treatment. While this type of tumor can be regarded as practically benign, since metastasis is virtually unknown and recurrence is rare, on histologic grounds it must be considered as a true sarcoma. We encountered only five cases of such tumor in our series; the average age of the patients was 38 years and the average duration of the tumor three and five-tenths years. One case was of special interest, as the tumor developed in the scar of a rectus incision. Resection of the entire large intestine had been carried out in a 22 year old woman for multiple polyposis with three distinct carcinomas of the large intestine. Three years after this series of operations the desmoid tumor developed in the scar.

A consideration of adenofibrosarcoma of the breast (table 12) perhaps does not belong in a discussion of fibrosarcoma in general; this tumor has been considered in a number of careful treatises. However, the seventeen cases encountered in this series are of sufficient interest to be placed on record in a rather cursory fashion. The average age of the patients was 54 years. All were females. Thirteen patients are living and well; one was lost for follow up; one died without disease after one and one-half years, and one died with disease seven months after the onset. The case of the patient who was lost for follow up is of great interest. An adenofibroma of each breast was removed by bilateral amputation five years before the development of the present tumor, which appeared in the scar. It is interesting to speculate whether this might have arisen from aberrant breast tissue or from a persistent remnant of one of the adenofibromas previously removed. The former possibility is strengthened by the location of the growth in the lateral portion of the scar. A point of practical importance is that of the eight patients on whom a radical amputation was done, including dissection of the axillary nodes, none showed any evidence of involvement of the lymph nodes.

Adenofibrosarcoma of the breast occurs at a considerably later age than does adenofibroma, and consequently the chief problem in differential diagnosis is to distinguish it from carcinoma. Because of its failure to metastasize to the axillary nodes this differentiation is of great practical importance. The gross appearance of such a tumor is helpful in differentiating it from carcinoma. It is usually large; it expands the surrounding tissue rather than shows the bands of stromal contraction characteristic of carcinoma; it is freely movable, even after it has reached a fair size, and on section it is soft and often succulent, sometimes with a translucent appearance and a somewhat botryoid tendency. From the extent of the tumors noted in our series we feel that the procedure of choice is simple amputation of the breast, with removal of the fascia overlying the pectoralis muscle. We have included one case in the group (17) that of a woman 67 years of age, whose tumor

TABLE 12.—*Adenofibrosarcoma of the Breast*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Results: Alive and Well, Years	Results: Living With Disease	Results: Died Without Disease, Years	Results: Died With Disease	Pathologic Diagnosis
1	74	♀	1	?	Right breast	Excision	0	0	1.4	1.5	...	..	1.4	..	Fibrosarcoma with tumor giant cells
2	34	♀	6	Large	Left breast	Excision	0	0	...	...	...	..	..	..	Adenofibrosarcoma
3	49	♀	8	Large	Right breast	Excision	0	0	2.8	3.5	2.8	..	..	..	Adenofibrosarcoma
4	51	♀	36	Large	Left breast	Radical operation	0	0	3.8	6.8	3.8	..	..	..	Adenofibrosarcoma with tumor giant cells
5	50	♀	12	Large	Left breast	Radical operation	0	0	4.2	5.2	4.2	..	..	..	Adenofibrosarcoma
6	39	♀	?	Small	Right breast	Amputation; roentgen rays	0	0	4.0	4.0	4.1	..	..	..	Adenofibrosarcoma
7	48	♀	?	Large	?	Radical operation	0	0	3.3	3.3	3.3	..	..	..	Adenofibrosarcoma
8	66	♀	12	Large	Left breast	Amputation; roentgen rays; radium	0	0	1.8	2.8	1.8	..	..	..	Adenofibrosarcoma
9	60	♀	1	Large	Right breast	Radical operation	0	0	2.2	2.3	2.2	..	..	..	Fibrosarcoma with tumor giant cells
10	42	♀	4	Large	?	Operation	0	0	0.3	0.6	...	..	..	+	Fibrosarcoma with tumor giant cells
11	59	♀	6	Small	Left breast	Radical operation	0	0	1.5	2.0	1.5	..	..	..	Adenofibrosarcoma
12	58	♀	0.5	Small	Right breast	Excision; roentgen rays	0	0	1.0	1.0	1.0	..	..	..	Adenofibrosarcoma
13	47	♀	1	Large	Right breast	Excision	0	0	1.0	1.1	1.0	..	..	..	Adenofibrosarcoma
14	48	♀	1	Large	Left breast	Radical operation	0	0	1.0	1.1	1.0	..	..	..	Adenofibrosarcoma
15	60	♀	3	Small	Left breast	Radical operation	0	0	3.4	3.6	3.4	..	..	..	Adenofibrosarcoma
16	60	♀	3	Large	Right breast	Radical operation	0	0	7.0	7.2	7.0	..	..	..	Adenofibrosarcoma
17	67	♀	?	Small	?	Radical operation	0	0	0.8	0.8	0.8	..	..	..	Neurogenic fibrosarcoma

TABLE 13.—*Cases of Fibrosarcoma of Special Interest*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Results: Alive and Well, Years	Results: Living With Disease	Results: Died Without Disease	Results: Died With Disease	Pathologic Diagnosis
1	25	♂	12	Large	Upper part of left thigh	Roentgen rays	0	+	6.5	7.5	...	..	..	+	Fibrosarcoma
2	64	♀	1 (?)	Large	Neck	Operation	..	..	...	...	...	..	..	..	Fibrosarcoma
3	48	♂	?	Small	Penis	Operation	2	+	0.6	0.6	...	..	..	+	Fibrosarcoma; also epidermoid carcinoma, grade I
4	62	♂	?	Small	Left side of nose	Operation	0	0	0.8	0.8	0.8	..	..	..	Fibrosarcoma; also basal cell carcinoma
5	74	♀	2 (?)	Small	Left side of chest	Operation	0	0	3.2	3.5	3.3	..	..	..	Fibrosarcoma; also epidermoid carcinoma, grade III

was somewhat suggestive of neurogenic fibrosarcoma rather than of adenofibrosarcoma. Certain tumors, purely fibroblastic, are undoubtedly growths in which the overgrowth of the connective tissue element has wiped out the glandular structure and has made them appear as fibrosarcomas. The gross characteristics and the clinical behavior of these tumors are in keeping with the adenofibrosarcoma rather than the fibrosarcoma of the trunk.

We have regarded five cases (table 13) as worthy of special attention and grouping, regardless of the location of the growth. The first (case 1) is that of a man, 25 years of age, in whom a benign giant cell tumor of the upper part of the left femur developed, with later involvement of the ilium. This tumor ultimately developed into a fibrosarcoma, and the patient died with disease seven and five-tenths years after the onset. This case has been reported in detail by Simmons.[8]

In another case (2) a fibrosarcoma developed in a woman 64 years of age in the scar left by lymphadenitis following measles that occurred in childhood. This scar had been extensively treated with tri-nitrophenol fifteen years before the development of the sarcoma, and it may perhaps be assumed that this stimulation, which had produced a severe burn, was the initiating factor in the development of the neoplasm.

In still another case the sarcoma arose in the stroma of an epidermoid carcinoma of the penis that had been treated unsatisfactorily in a piecemeal fashion over a period of five and one-half years. Ultimately fibrosarcoma of the stroma developed, being found by chance at amputation of the penis for the recurrent carcinoma. The sarcoma promptly recurred and metastasized widely, killing the patient with multiple metastases six-tenths year after its detection.

In the two remaining cases the tumor developed on the basis of roentgen and radium burns. The development of carcinoma from roentgen lesions is well recognized, while that of fibrosarcoma is less frequent and is ordinarily not given great weight in the differential diagnosis of postradiation cutaneous changes. In all these cases the tumor developed later after the initial irradiation, in one case occurring after fourteen years of roentgen and radium treatment of a basal cell cancer of the nose, and in another (case 5) occurring together with epidermoid carcinoma of the skin twenty-four years after roentgen treatment of a tumor of the breast. One other case, in which the tumor was at first diagnosed as fibrosarcoma and epidermoid carcinoma, was that of one of the pioneer roentgen workers, a man 52 years of age who had received roentgen burns twenty-three years before. He had had several fingers amputated. In this case there was involvement of both the epitrochlear and the axillary lymph nodes, there having been two operations for involvement

8. Simmons, C. C.: Surg., Gynec. & Obst. **53**:469, 1931.

of the epitrochlear nodes and one for involvement of the axillary lymph nodes, followed by amputation of the shoulder joint. However, careful study has convinced us that this tumor is properly classified as one of the spindle cell carcinomas recently reported by Martin and Stewart.[9]

SUMMARY AND CONCLUSIONS

Data for one hundred and sixty-three cases of fibrosarcoma of the soft parts have been analyzed and presented.

Fibrosarcoma is not a disease of young persons, the mean age at onset in both sexes being about 50 years.

Trauma is not an etiologic factor in these cases.

Most patients have been treated by operation.

Radiation therapy has been disappointing.

The interval from the onset of symptoms to the beginning of treatment bears no definite relation to the outcome of the treatment.

The neurogenic fibrosarcoma may be recognized as a definite subtype.

The appearance of tumor giant cells indicates higher malignancy, as was evidenced by a higher mortality and a shorter duration of the disease in the cases studied.

Recurrence is frequent (sixty-four cases) and has grave prognostic significance. However, eight patients are alive and well three years after treatment of their last recurrence.

Recurrence usually is early and is rare after the first year.

Metastasis is infrequent (thirty-four cases) and usually occurs after local recurrence.

Metastasis is most frequent in the lungs and may involve regional lymph nodes.

Fibrosarcoma involving the head or neck is serious, only 21 per cent of our patients being alive and well three or more years after the onset.

Seventeen cases of adenofibrosarcoma of the breast are reported; all but one of the patients have recovered. Lymph nodes were not involved.

In two cases fibrosarcoma was apparently secondary to changes caused by irradiation.

Ten instances of multiple tumor were found—6 per cent of the total number.

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9. Martin, H. E., and Stewart, F. W.: Am. J. Cancer **24**:273, 1935.

EFFECT OF FAT INTRODUCED INTO THE JEJUNUM BY FISTULA ON MOTILITY AND EMPTYING TIME OF THE STOMACH

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Although considerable experimental work has been done in the last decade on the question of inhibition of gastric motility by fat, with very suggestive results, little of this research has made use of the barium sulfate meal and fluoroscope. Because this method offers the best approach to normal conditions, with no disturbance of the nervous or muscular continuity of the stomach, it appears to be a logical means by which to observe this phenomenon of inhibition. Accordingly, making use of the barium sulfate meal and fluoroscope and with dogs as subjects, I undertook the study now reported. Since the upper portion of the small intestine is believed to be the site of formation of the inhibitory agent, I studied the effect produced on the emptying of a barium sulfate meal from the stomach by fat introduced into the jejunum by way of a fistula. The influence of various control substances in the jejunum was determined, and a comparison was made between the action of fat in the small intestine and that of fat in the stomach. The study was made under the direction of Dr. F. C. Mann and Dr. J. L. Collman.

The discovery that fats retard digestion can scarcely be said to be one of the contributions of modern medicine, since Aristotle [1] wrote of it; however, Ewald and Boas [2] (1885-1886) were apparently the first to enlighten the medical profession with accurate experimental data on this subject. They determined, by aspiration of the gastric contents at inhibited for two hours in the cul-de-sac when oil was placed in the greater various periods after a starch-paste test meal with and without oil had been given, that when the mixture contained oil digestion was delayed

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1. Aristotle, quoted by Cowie, D. M., and Munson, J. F.: An Experimental Study of the Action of Oil on Gastric Acidity and Motility, Arch. Int. Med. **1**:61-101 (Jan.) 1908.

2. Ewald, C. A., and Boas, J.: Beiträge zur Physiologie und Pathologie der Verdauung, Virchows Arch. f. path. Anat. **101**:325-375, 1885; Beiträge zur Physiologie und Pathologie der Verdauung: II., ibid. **104**:271-305, 1886.

and that free acid was rarely present within the first half hour after the meal was taken. They concluded that the oil was responsible for the deficiency in hydrochloric acid and that the strength of the hydrochloric acid bore a relation to the rapidity of emptying of the stomach.

Lobasov,[3] according to Pavlov,[4] experimenting in 1897 on dogs with esophageal and gastric fistulas and Pavlov pouches, showed that the nervous phase of gastric secretion in response to a sham meal was inhibited for two hours in the cul-de-sac when oil was placed in the greater stomach. Lintwarew [5] in 1903 found in dogs with duodenal and gastric fistulas that fat introduced either into the stomach or into the duodenum caused reflex closing of the pyloric sphincter for from 1 to 3 hours. He postulated that this effect of fat was chemical and not mechanical. Sokolov,[6] according to Babkin,[7] in 1906 prepared dogs by making both a gastric and a duodenal fistula and a Pavlov pouch in each and by excising the portion of stomach and duodenum between the two fistulas so that material in the stomach could not gain entrance to the duodenum. He found in these animals a marked variation in the effect of fat on gastric secretion produced in the Pavlov pouch by meat in the stomach depending on whether the fat was placed in the stomach or in the duodenum. There was no effect on secretion in the pouch when fat was placed in the stomach, but there was marked inhibition of secretion when fat was placed in the duodenum. Lönnqvist [8] corroborated this work shortly afterward and thus strengthened Sokolow's view that the inhibitory effect of fat arises in the duodenum and that not only the nervous phase of secretion but the gastric phase as well is inhibited by this agent. Pavlov, after correlating the work done in his laboratory by Lobasov, Lintwarew, Sokolow and Lönnqvist, explained this property of fat as "a reflex inhibition of the secretory process, the reflex not necessarily originating in the stomach." He doubted the mechanical explanation.

Cannon [9] in 1904, in his epochal experiments on digestion in cats, noted by means of the barium sulfate meal and fluoroscope that the average rate per minute of gastric peristalsis after a fat meal was

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3. Lobasov, I. O., quoted by Pavlov.[4]

4. Pavlov, I. P.: The Work of the Digestive Glands, ed. 2, London, Charles Griffin & Company, Ltd., 1910.

5. Lintwarew, S. J.: Ueber die Rolle der Fette beim Uebergang des Mageninhalts in den Darm, Biochem. Centralbl. **1**:96-97 (Jan. 15) 1903.

6. Sokolow, quoted by Babkin.[7]

7. Babkin, P. B.: Die äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1914.

8. Lönnqvist, Bernt: Beitrag zur Kenntnis der Magensaftabsonderung, Skandinav. Arch. f. Physiol. **18**:194-262, 1906.

9. Cannon, W. B.: The Passage of Different Food-Stuffs from the Stomach and Through the Small Intestine, Am. J. Physiol. **12**:387-418 (Dec.) 1904. The Mechanical Factors of Digestion, New York, Longmans, Green & Co., 1911.

slightly less and the waves more shallow than when proteins or carbohydrates were ingested. In his classic work on hunger in 1916 Carlson [10] observed that oil as well as other substances introduced into the small intestine inhibited gastric hunger contractions and gastric tonus.

During the course of some experiments in 1925 on gastric secretion in dogs with the stomach and duodenum separated (Lönnqvist-Pavlov and Lönnqvist-Heidenhain pouches), Lim, Ivy and McCarthy [11] observed that the application of as much as 250 cc. of olive oil to the entire stomach did not affect the course of secretion. However, fat in the duodenum inhibited the secretion of the entire stomach pouch which was stimulated mechanically by distention with a balloon. Inhibition of motility in the autotransplanted pouches of dogs produced by placing fat in the main portion of the stomach led Farrell and Ivy [12] in 1926 to postulate with favorable experimental background that a humoral mechanism is responsible for such inhibition by fat. In a similar manner Feng, Hou and Lim [13] in 1929 demonstrated the inhibition of gastric secretion in autotransplanted pouches, and they came to the same conclusion as to the nature of the production of such inhibition.

That bile might be intimately concerned in the inhibition of gastric motility by fat was suggested when Still and Carlson [14] in 1929 produced immediate but temporary inhibition and great diminution of gastric secretory response to a test meal by intravenous injection of bile. However, Kosaka and Lim [15] in 1930 were unable to demonstrate such inhibition even with intravenous injection of toxic doses of bile.

Feng, Hou and Lim in 1929 injected into a vein of a dog with an autotransplanted stomach pouch lymph taken from the thoracic duct of another dog that had been fed a fat meal previously and observed no inhibition of gastric secretion in the pouch. Moreover, fat still inhibited the gastric motility of an animal with a fistula of the thoracic duct.

10. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

11. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. E.: Contributions to the Physiology of Gastric Secretion: I. Gastric Secretion by Local (Mechanical and Chemical) Stimulation, Quart. J. Exper. Physiol. **15**:13-53, 1925.

12. Farrell, J. I., and Ivy, A. C.: Studies on the Motility of the Transplanted Gastric Pouch, Am. J. Physiol. **76**:227-228, 1926.

13. Feng, T. P.; Hou, H. C., and Lim, R. K. S.: Mechanism of Inhibition of Gastric Secretion by Fat, Chinese J. Physiol. **3**:371-380 (Oct.) 1929.

14. Still, Kathleen S., and Carlson, A. J.: The Motor and Secretory Activity of the Stomach During Acute and Chronic Obstructive Jaundice in Dogs, Am. J. Physiol. **89**:34-45 (June) 1929.

15. Kosaka, T., and Lim, R. K. S.: On Mechanism of Inhibition of Gastric Motility by Fat: Inhibitory Agent from Intestinal Mucosa, Chinese J. Physiol. **7**:5-11 (March 15) 1933.

These investigators concluded that the extrinsic nerves of the stomach were not essential in this inhibition by fat and suggested a humoral mechanism as the more logical explanation; also, that fat itself was not the inhibitory agent and that the agent was not transmitted through lymphatic channels.

Roberts [16] in 1931, working with normal subjects and with patients suffering from gastric disorder in various forms, confirmed the fact, by aspiration of a previously fed gruel meal, that oil inhibits gastric secretion and motility. He proved that the slow emptying was not secondary to the inhibition of secretion, and he believed that a colyone resulted from absorption of the oil in the duodenum which exerted a restraining influence on the gastric cells and motility.

Nothmann and Wendt [17] in 1932, using the barium sulfate meal and fluoroscope, with dogs as the subjects, found that olive oil delayed markedly the emptying time of the stomach. Ligation of the pancreatic ducts did not affect this normal reaction to fat. Following total pancreatectomy oil had no inhibitory action on the motility of the stomach, and it disappeared from the stomach in a shorter time than proteins, the disappearance of which was also slightly faster than normal. Insulin had no inhibitory effect on this rapid emptying of the stomach. A barium sulfate meal without fat left the stomach in the usual time after extirpation of the pancreas. Nothmann and Wendt concluded that inhibition by fat is regulated by the pancreas, and that it prevents overloading of the duodenum with fat. Since the nerves to the pancreas were necessarily disturbed by the operative procedure, the investigators could not determine whether this effect was of a hormonal or a nervous nature.

Kosaka and Lim [18] in 1930 prepared an olive oil extract of the upper part of the small intestine which on intravenous or subcutaneous injection inhibited gastric secretion following a test meal. Similar extracts made from the gastric mucous membrane were without effect. Continuing their experiments, Kosaka, Lim, Ling and Liu [19] in 1932 prepared a trinitrophenol concentrate of the aforementioned extract, which

16. Roberts, W. M.: The Effect of Oils on Gastric Secretion and Motility, Quart. J. Med. **24**:133-152 (Jan.) 1931.

17. Nothmann, M., and Wendt, H.: Ueber eine regulatorische Funktion des Pankreas für die Magenentleerung nach Fettmahlzeit, Arch. f. Exper. Path. u. Pharmakol. **168**:49-56, 1932.

18. Kosaka, T., and Lim, R. K. S.: Demonstration of the Humoral Agent in Fat Inhibition of Gastric Secretion, Proc. Soc. Exper. Biol. & Med. **27**:890-891, (June) 1930.

19. Kosaka, T.; Lim, R. K. S.; Ling, S. M., and Liu, A. C.: On Mechanism of Inhibition of Gastric Secretion by Fat: Gastric-Inhibitory Agent Obtained from Intestinal Mucosa, Chinese J. Physiol. **6**:107-126 (Feb. 15) 1932.

they found to be most potent. They suggested that the inhibitory substance is for the most part present in normal intestinal mucosa in an inactive state and that after exposure to oil a certain proportion of the inactive substance is activated. They proposed that the substance be called "enterogastrone." In 1933 Kosaka and Lim,[15] using the trinitrophenol preparation from the upper part of the small intestine intravenously, found gastric motility inhibited in dogs with gastric fistulas studied by the balloon method. However, the action of the preparation did not even approximate the inhibition produced by oil given by mouth. They suggested that possibly the enteric reflexes entered into the inhibition as well as the chemical mechanism, so that the latter acting alone could not be expected to produce as marked a result as oil by mouth.

Quigley, Zettelman and Ivy[20] in 1934 determined by the balloon method that the intravenous introduction of fat, soap, glycerin and chyle from the thoracic duct, respectively, was without effect on the gastric motility of dogs. By giving five times the threshold doses of cholecystokinin and secretin, respectively, and observing the absence of alteration in gastric motility they demonstrated that these two substances are apparently not concerned in the mechanism of inhibition by fat. When the extrinsic nerves were removed as completely as possible from a dog's stomach the latent period in the response to fat was found to be slightly longer (4 minutes) than when the nerves were intact (1½ minutes). They also demonstrated by various operative procedures that the site of initiation is dependent on contact of the oil with the mucosa of the upper part of the small intestine. They concluded that inhibition of gastric motility by fat undoubtedly involves a humoral agent, probably a colyone, and that, although under normal circumstances both the nervous and humoral mechanisms are perhaps involved in the process, the latter can act in the absence of the former, a longer latent period being the only difference.

In 1933 Lim,[21] summarizing the results of research on the subject, concluded that fat inhibits gastric motility and both the nervous and chemical phases of gastric secretion. Neither a reflex adrenal secretion nor a nervous reflex is essential in the mechanism. He believed this to be a chemical process and that the agent would be found in the intestine. Lim postulated that one colyone is responsible for the inhibition of both gastric secretion and gastric motility by fat.

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20. Quigley, J. P.; Zettelman, H. J., and Ivy, A. C.: Analysis of the Factors Involved in Gastric Motor Inhibition by Fats, Am. J. Physiol. **108**:643-651 (June) 1934.

21. Lim, R. K. S.: Observations on the Mechanism of the Inhibition of Gastric Function by Fat, Quart. J. Exper. Physiol. **23**:263-268, 1933.

MATERIAL AND METHOD OF STUDY

Six normal, healthy adult dogs, three males and three females, ranging in weight from 7 to 22 Kg., were used in these experiments.

Operation.—The jejunum was transected 14 cm. distal to the ligament of Treitz. To produce a jejunal fistula the portion of intestine distal to the transection was brought to the skin in the superior part of the abdominal incision. After closing the proximal end of the transected jejunum, a side-to-side anastomosis was made between it and the other portion of jejunum about 25 cm. distal to the stoma of the fistula (fig. 1). The lumen of the anastomosis was about three times as large as the intestine at this point. All operations were performed under

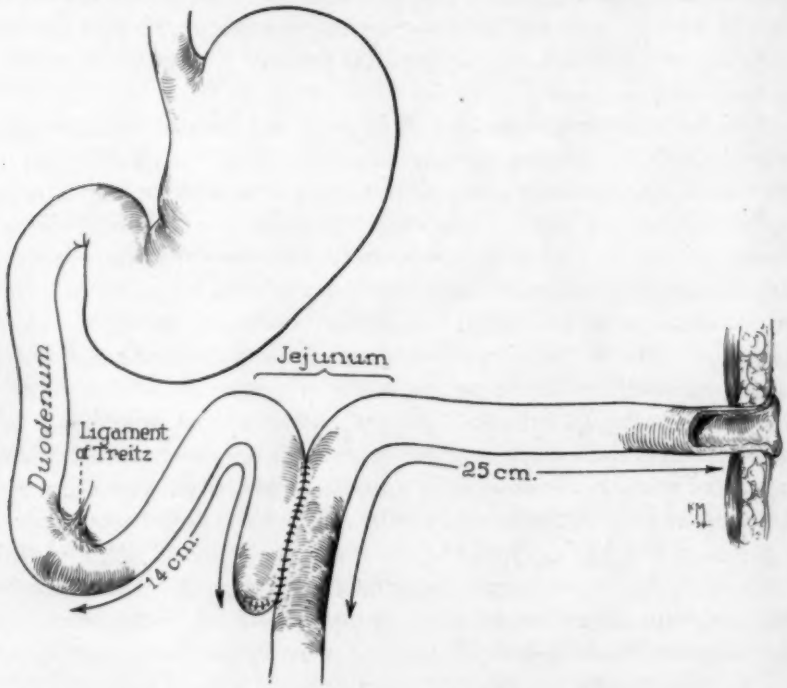

Fig. 1.—Method of making a jejunal fistula.

ether anesthesia, using surgical technic. All the dogs made an uneventful convalescence, and there was scarcely any leakage from the fistula; the dogs exhibited no signs or symptoms referable to the operative procedure and were apparently in normal health.

Training.—The dogs were made familiar with the observer, the passage of the stomach tube and the noises peculiar to the use of the fluoroscope. On no dog was an experiment begun until it was apparent that the animal was thoroughly familiar with the whole process; this required usually from 3 to 4 weeks of training. The dog was examined on the fluoroscopic table with loose restraining ropes on all four legs to hold it in position on its back. All the dogs remained quiet and composed during examination and made no effort to free themselves.

Feeding and Care.—The dogs were fed once daily by the observer a mixture of horse meat and cracker crumbs of twice the respective caloric requirement

for each dog at rest. They were taught to eat this meal immediately, and the food pan was shortly removed from the cage so that each animal was without food for 24 hours prior to the experiment. The dogs were fed at the same hour each day, except on those days on which observations were made, when they were fed at the completion of the experiment. No animal was put through the procedure oftener than every 48 hours. They were allowed water until 15 minutes prior to the introduction of the barium sulfate meal, but none after this time until emptying of the stomach was complete.

Experimental Procedure.—Each experiment was therefore started after the animals had been on a 24 hour fast. Thus the barium sulfate meal was given at the same time that the dog was usually fed. The opaque mixture was freshly made just prior to its introduction, and the amount was determined by the weight of the animal, 15 Gm. per kilogram of body weight being given. It was composed, by weight, of one-third barium sulfate, one-third acacia (10 per cent) and one-third skimmed milk (twenty-four hours old). These proportions of the ingredients produced a liquid mixture which readily ran down the lumen of a stomach tube of ordinary size. This mixture is referred to subsequently as the routine meal, and it was used in experimental series A, B, C, D and F. In series E the same amount of cream was incorporated with the barium sulfate meal as had been given by way of the fistula in series D; it was substituted for the skimmed milk in the mixture, so that the total volume was the same as that of the routine meal just described. However, the introduction of the cream into this mixture in series E produced such a thick gruel as to hinder the passage of the meal down the stomach tube. This necessitated reducing the barium sulfate portion by a third, which gave a meal of almost identical consistency with the routine meal.

All the animals were given the barium sulfate meal by tube. One dog would take the mixture voluntarily, thus affording an opportunity to compare the two methods of introduction as to any effect on the emptying of the stomach; no constant difference was noted. The amounts of the various substances placed in the jejunal fistula were determined also by the respective weights of the animals, approximately 5 Gm. per kilogram of body weight being used (100 Gm. for the two larger dogs, 50 Gm. for the two medium-sized dogs and 35 Gm. for the two smaller dogs). The material was always inserted into the fistula immediately prior to the barium sulfate meal in the stomach, never more than five minutes elapsing between the two maneuvers.

After the mixture had been placed in the stomach the animals were immediately examined fluoroscopically to determine the time of the first passage of material into the duodenum. If this did not occur within 10 minutes the dogs were returned to their cages and were examined at intervals of 15 minutes until the time of appearance of barium sulfate in the duodenum was determined. The dogs were then examined fluoroscopically every hour until the stomach was almost empty, after which they were examined at intervals of 30 minutes to determine as accurately as possible the gastric emptying time. Between observations the dogs were always placed in their cages in their usual surroundings.

RESULTS

Series A: Determination of the Normal Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach.—After the postoperative convalescence and training period were com-

plete, the normal emptying time of the routine barium sulfate meal was determined for each of the six dogs by five satisfactory experiments. In series A nothing was inserted into the jejunal fistula.

The time of appearance of barium sulfate in the duodenum ranged from 4 to 33 minutes in the different animals, the average for each varying between 4.4 and 23.4 minutes. With the exception of one dog (M 195), the averages fell between 4.4 and 9.2 minutes, which is fairly uniform. The average emptying time with this mixture varied between 2 hours and 4.6 minutes and 3 hours and 31.6 minutes, the stomachs of the heavier dogs with the larger meals requiring longer to empty. Some of the animals were strikingly uniform in regard to the emptying

A Comparison of the Average Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach (Series A, B, C, D and E)

Dog	Weight, Kg.	Quantity in Fistula, Cc.		Series A		Series B		Series C		Series D		Series E	
				Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
M 447	22	100	AP*	..	9.2	..	8.2	..	19.8	..	111.0	..	12.6
			ET†	3	31.6	4	36.8	4	18.8	8	12.0	7	36.6
M 690	18	100	AP*	..	8.0	..	9.4	..	18.2	..	98.0	..	14.0
			ET†	3	7.0	3	5.0	2	57.2	6	24.0	6	3.6
R 543	11	50	AP*	..	6.0	..	7.0	..	8.0	..	52.6	..	11.6
			ET†	2	36.0	3	5.0	2	51.8	5	45.6	5	7.2
R 377	10	50	AP*	..	6.6	..	6.4	..	17.8	..	58.0	..	14.4
			ET†	2	34.2	2	38.0	2	44.8	4	8.0	4	13.4
M 195	7	35	AP*	..	23.4	..	12.8	..	18.0	..	80.0	..	9.0
			ET†	2	48.4	2	38.8	2	58.0	5	9.0	4	54.0
R 540	7	35	AP*	..	4.4	..	7.6	..	10.6	..	44.6	..	8.2
			ET†	2	4.6	2	18.0	2	24.6	4	44.6	5	6.0

* AP means appearance time; i. e., the time until barium sulfate was first seen passing down the duodenum.

† ET means emptying time; i. e., the time until the stomach was empty.

time of the stomach (R 540). One dog (M 690) varied as much as 1 hour from its average in one of the experiments (table and fig. 2).

Van Liere and Crisler[22] found the normal emptying time of the dog's stomach as observed by the fluoroscope to be remarkably uniform from day to day when all factors were kept constant. The extremes for a group of dogs varied from 5.42 to 8.07 hours, but these figures cannot be satisfactorily compared with mine since Van Liere and Crisler incorporated barium sulfate with a protein meal whereas the opaque mixture used in my experiments was comparatively inert. Ivy and Fauley,[23] using a different opaque mixture after a 24 hour fast, found the emptying of the dog's stomach as observed by the fluoroscope to vary from 4 hours and 10 minutes to 5 hours and 17 minutes.

22. Van Liere, E. J., and Crisler, G.: Normal Emptying Time of the Stomach of the Dog, Proc. Soc. Exper. Biol. & Med. **31**:85-87 (Oct.) 1933.

23. Ivy, A. C., and Fauley, G. B.: The Effect of Hunger on the Emptying Time of the Stomach, Am. J. Physiol. **91**:206-209 (Dec.) 1929.

Series B: The Effect on the Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach Produced by Placing Physiologic Solution of Sodium Chloride in the Jejunum.—The procedure in this series of experiments differed from that in series A only in that varying amounts of physiologic solution of sodium chloride (35 to 100 cc., depending on the weight of the animal)

Fig. 2 (series A).—Emptying of the routine meal from the stomach. Nothing was introduced into the jejunal fistula. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower right, 4 hours.

were placed in the jejunum by way of the fistula by slow injection through a soft rubber catheter. This immediately preceded the giving of the routine meal. Observations on the appearance time and emptying time were made exactly as in series A. The procedure was repeated for each animal until five satisfactory experiments were completed. The time of appearance of barium sulfate in the duodenum ranged from

5 to 21 minutes, the averages falling between 6.4 and 12.8 minutes. The average emptying time of the stomach varied between 2 hours and 18 minutes and 4 hours and 36.8 minutes for the different animals, which again demonstrated fair uniformity in the individual trials for each dog except for the experiments on the two larger animals, in which the emptying time varied 1 hour from the average (table).

In series B, in the majority of cases, there was a slight delay in the time of appearance of barium sulfate in the duodenum and a slight prolonging of the emptying time of the stomach as compared with the observations in series A. Since this delay was so insignificant and was not constant in all the dogs one must conclude that physiologic solution of sodium chloride in the jejunum as used in these experiments had little if any effect on gastric motility and emptying time.

Series C: The Effect on the Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach Produced by Placing Skimmed Milk in the Jejunum.—Since the study of the inhibitory effect produced by fat in the jejunum was the primary object of these experiments, skimmed milk should be the ideal control to the cream used in the next series of experiments, D, as the only material difference between these two was in the higher fat content of the latter.

The procedure in this series of experiments differed from that in series B only in that skimmed milk was placed in the fistula instead of physiologic solution of sodium chloride. The appearance time varied from 5 to 32 minutes, the averages falling between 8 and 19.8 minutes. The emptying time averaged from 2 hours and 24.6 minutes to 4 hours and 18.8 minutes, likewise being fairly uniform from experiment to experiment in each case except in the largest animal, in which on one occasion the time varied by 80 minutes. There was a delay in the appearance time varying from 1 to 11.6 minutes in the different dogs, with an average delay of 6.8 minutes. In spite of this, there was no constant significant delay in emptying time when milk was used in place of physiologic solution of sodium chloride in the jejunal fistula (table and fig. 3).

In support of this delay in appearance of the barium sulfate, it is interesting that Carlson found that 10 cc. of milk (it was not stated whether it was whole or skimmed) in the duodenum inhibited hunger contractions in dogs for 30 minutes, which was longer than with any of the other substances tried. Thus it appears that skimmed milk introduced into the jejunal fistula definitely delays the first appearance of barium sulfate in the duodenum but has no appreciable constant effect on the time required for complete evacuation.

Series D: The Effect on the Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach Produced by Placing Cream (16 Per Cent Fat) in the Jejunum.—The procedure in this series of experiments differed from that in series C only in the introduction of cream into the fistula just prior to the giving of the barium sulfate mixture by tube.

Fig. 3 (series C).—Emptying of the routine meal from the stomach after skimmed milk was placed in the jejunal fistula. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower right, 4 hours.

At the first fluoroscopic examination, made within 5 minutes after the passage of the barium sulfate meal down the tube, there was marked atony of the whole stomach, and no peristaltic waves were discernible. This was in marked contrast to the usual findings with the preceding control meals (series A, B and C) in which active peristalsis, especially over the antral portion, was always present at this period and continued uninterrupted until emptying of the stomach was complete. With cream

in the jejunum, peristalsis did not appear until from 30 to 90 minutes (depending on the individual dog) after the entrance of the meal into the stomach. During the first few minutes the peristaltic waves were very shallow and never appeared throughout the delayed evacuation of the stomach to reach the depth they did in the first three series of controls.

The time of appearance of the barium sulfate in the duodenum was markedly delayed as compared with that in the control series A, B and C. The longest delay was 135 minutes; the shortest, 38 minutes. The average of the five experiments for each of the dogs ranged between 44.6 and 111 minutes. The total average delay in the appearance time for all the dogs caused apparently by fat in this series of experiments was 58.6+ minutes longer than that caused by the skimmed milk given in series C (table and fig. 4). The emptying time of the stomach was also markedly delayed by cream in the jejunum, being roughly almost 100 per cent longer than the time required in the control series (A, B and C). Compare figure 4 with 2 and 3. The emptying of the animals' stomachs was complete in from 3 hours and 50 minutes to 9 hours and 10 minutes. The averages for the respective dogs ranged between 4 hours and 8 minutes and 8 hours and 12 minutes.

It is quite important to note in series D that in spite of the handling on the fluoroscopic table and the frisking about of the dogs to and from their cages barium sulfate never was seen in the duodenum in less than 38 minutes. This seems to indicate that the inhibitory mechanism produced by fat owes part of its effect on the stomach to actual closure of the pyloric sphincter in addition to the atony and absence of peristalsis. If closure of the pylorus did not occur, some of the barium sulfate mixture would have been splashed or forced down the duodenum by gravity or by movements of the animal prior to this 38 minute period.

It is significant that Quigley, Zettelman and Ivy produced inhibition of hunger contractions in the dog for 40 minutes by placing cream in the jejunum. Thus it appears that fat in the jejunum causes marked delay in the initial appearance in the duodenum of material from the stomach as well as complete absence of peristalsis, giving way later to shallow waves that never reach the normal depth during evacuation. The emptying time is markedly delayed, and actual closure of the pylorus as part of the gastric inhibitory mechanism seems to be produced.

Series E: The Effect on Gastric Motility and Emptying Time Produced by Incorporating Fat with the Barium Sulfate Mixture in the Stomach.—The same amounts of cream were mixed with the barium sulfate meal as had been placed in the respective fistulas in series D. This cream was substituted for the skimmed milk used in the prepara-

tion of the routine meal, and the barium sulfate was cut down slightly until the volume and consistency of the meal were the same as those of the routine meal, and hence the meals could be compared. Nothing was introduced into the fistulas.

The first fluoroscopic examination after 5 minutes revealed active peristalsis of a good grade comparable to that in the control experiments. The time of appearance of barium sulfate in the duodenum varied in the different animals between 5 and 30 minutes, averages for the five experiments falling between 8.2 and 14.4 minutes. This finding was

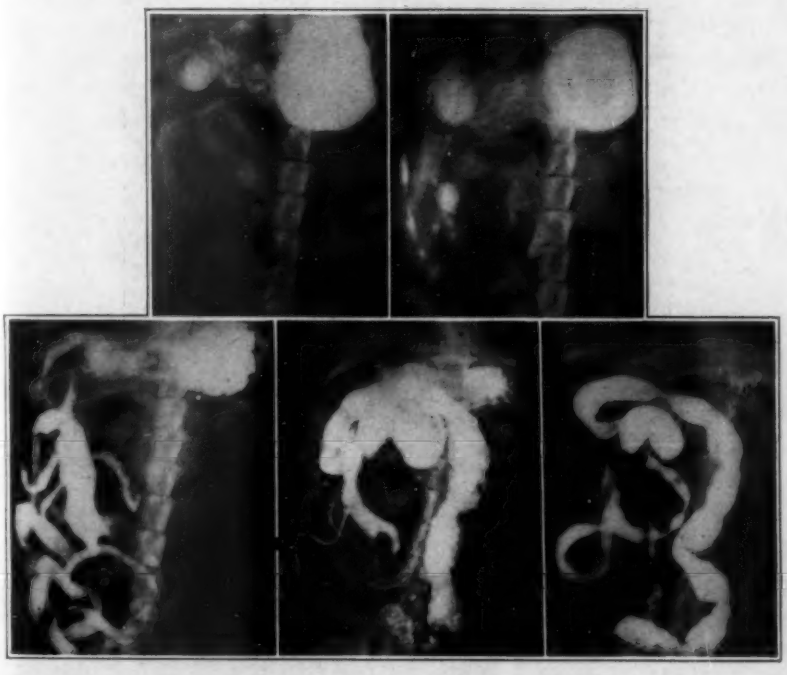

Fig. 4 (series D).—Emptying of the routine meal from the stomach after cream was placed in the jejunal fistula. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower middle, 5 hours; lower right, 6 hours.

in marked contrast to the lack of peristalsis and the delayed appearance in series D, and it indicates that fat in the jejunum has a much quicker and more profound inhibitory effect than the same amount of fat in the stomach. It was only after a considerable amount of this barium sulfate mixture containing fat had passed into the upper part of the small intestine (in from 15 to 30 minutes) that inhibition of gastric peristalsis and of emptying became apparent, but it never equaled that produced by the same amount of fat in the jejunum. Peristalsis of a degree diminished from the normal continued until emptying was com-

plete. The emptying time varied between 8 hours and 15 minutes and 3 hours and 35 minutes; the averages were between 4 hours and 13.4 minutes and 7 hours and 36.6 minutes and thus were not materially different from those in series D (table and fig. 5).

Comparing the observations in series E with those in series D, it is apparent that there is, first, a profound and immediate effect of fat in the jejunum and, second, that there is a delayed effect of fat when it is in the stomach until a portion of it has reached well down into the

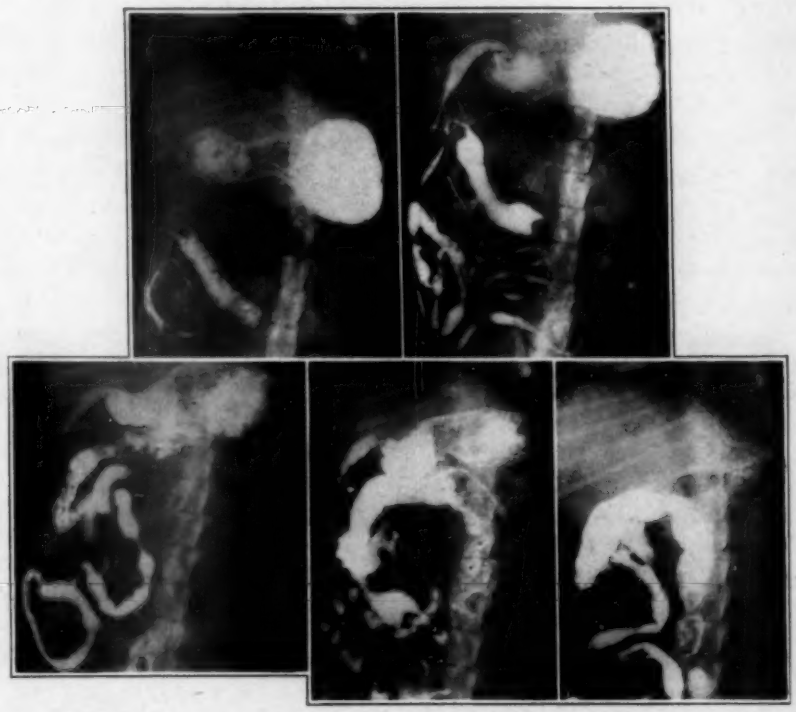

Fig. 5 (series E).—Emptying of a barium sulfate mixture of the same consistency and volume as the routine meal but in which was incorporated the same amount of cream as was used in series D. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower middle, 5 hours; lower right, 6 hours.

upper part of the small intestine. This in addition to its weaker effect points to the site of formation of the inhibitory agent being in the upper part of the small intestine and not in the stomach. This conclusion was previously reached by Sokolow, Lönnqvist, Ivy and Lim after operative procedures on animals in which the nervous and muscular continuity had been disrupted. The experiments in the present study, however, demonstrate this seat of action of fat with the organs and

nerves undisturbed by any surgical procedures and by a method that at present produces as nearly normal physiologic conditions in the stomach as possible.

The question may well be raised whether or not the difference in concentration of the cream in the barium sulfate mixture when it was diluted one-third (series E) as compared with the undiluted cream in the fistula (series D) might not account for this difference in action of the fat at the two sites. To rule out this possible source of error, two additional control experiments, series F and series G, were undertaken.

Series F: The Effect on the Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach Produced by Placing (1) Dilute Cream and (2) an Equivalent Quantity of Physiologic Solution of Sodium Chloride in the Jejunum.—In each phase of this experiment five trials were run on one dog (M 195); the routine meal was placed in the stomach, and the usual observations were made. Cream of the same dilution that resulted after its incorporation with the barium sulfate mixture in series E (in this case 35 cc. of cream was diluted to 105 cc. by physiologic solution of sodium chloride) was placed in the fistula just prior to introducing the meal into the stomach. There was no material difference in the degree of inhibition produced by this dilution compared with the average figures when undiluted cream was used. Further, for purposes of control, 105 cc. of physiologic solution of sodium chloride was introduced into the fistula in place of the diluted cream, to show that it was not the quantity of solution introduced that produced the inhibition. This amount of physiologic solution of sodium chloride did not produce any more appreciable inhibition than the 35 cc. used in series B and nothing comparable to the inhibition produced by diluted cream. Diluted cream therefore appears just as efficacious in producing inhibition in the jejunum as the same amount of undiluted cream, both having an equivalent content of fat.

Series G: The Effect on the Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach Produced by Placing Undiluted Cream in the Stomach.—Three animals were used in this series, and five experiments were completed on each animal. The same amount of undiluted cream was placed in the stomach by way of a tube as had been placed in each of the respective fistulas of the animals in series D. One-third the usual amount of barium sulfate was incorporated with the cream, which made the mixture easily visible with the fluoroscope and of the same consistency as the routine meal.

The time of appearance of the meal containing undiluted cream in the duodenum did not vary appreciably from the averages when diluted cream was used.

Thus, since it is clear from the experiments in series F and G that the concentration or dilution of the same amount of fat does not alter its inhibitory power, it must be concluded from the observations in series D and E that the site of initiation for the gastric inhibitory mechanism is not in the stomach but in the upper part of the small intestine.

Series H: The Effect on the Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach Produced by the Operative Procedure Used in Making the Jejunal Fistula.—One animal (R 540) was used for these observations. After it had been trained, five satisfactory experiments with the routine meal were run before operation. After postoperative convalescence was complete a similar set of observations was made in which nothing was introduced into the fistula. There was no appreciable difference noted in the time of appearance of the barium sulfate in the duodenum or in the emptying time of the stomach after the establishment of the jejunal fistula as compared with the preoperative observations.

SUMMARY

With trained animals under controlled conditions the time of appearance of the routine barium sulfate meal in the duodenum and the emptying time of the stomach were fairly uniform. Physiologic solution of sodium chloride in the jejunum as used in these experiments had little if any effect on gastric motility and emptying. Skimmed milk in the jejunum caused an average delay of 6.8 minutes in the first appearance of material from the stomach in the duodenum. It did not appreciably lengthen the time required for complete emptying of the stomach. Cream (fat) in the jejunum immediately produced marked atony of the whole stomach with no peristalsis for from 30 to 90 minutes, depending on the quantity introduced and the size of the animal. The time of appearance of barium sulfate in the duodenum was markedly delayed by fat in the jejunum, averaging 58 minutes longer than with skimmed milk, and the emptying time of the stomach was prolonged. The gastric inhibitory effect of fat placed in the stomach was much less pronounced than that of a similar quantity of fat placed in the jejunum. The fat was apparently without effect until it had reached the upper part of the small intestine. It is suggested by the observations that there is actual closure of the pylorus and that this plays an important rôle in gastric inhibition produced by fat in addition to atony and absence of peristalsis. These experiments, employing a method that does not disturb normal physiologic conditions in the stomach, demonstrate that fat initiates its inhibitory action in the upper part of the small intestine and not in the stomach.

SARCOMA OF THE STOMACH

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Frequently a pathologic condition considered rare in one generation and carefully studied and reported at that time appears to be more common in the following generation. The first case of sarcoma of the stomach was reported by Bruch [1] in 1847, and though subsequently many cases of this disease have been recorded in the literature, it is a relatively rare neoplasm which still eludes consideration from a diagnostic point of view, for in few of the reported cases was a diagnosis made before an operation or autopsy was performed. It is the object of this presentation to record a carefully studied case of sarcoma of the stomach in the hope that the correlation of the clinical data in this particular case with certain characteristic pathologic features of the disease may aid in its future clinical recognition.

The most comprehensive survey of the subject of sarcoma of the stomach which we have been able to find in the literature is that prepared by D'Aunoy and Zoeller,[2] who stated that 335 cases had been recorded up to and including the year 1929. They were able to review 135 case reports. Approximately 36 additional cases have been recorded since 1929, including 9 cases reported by Pack and McNeer [3] in May 1935. Balfour and McCann [4] presented the largest series from any one clinic, a group of 54 cases at the Mayo Clinic from January 1908 to July 1929. These 54 cases were extracted from a total of 4,159 cases of malignant lesion of the stomach, an incidence of 1 sarcoma to 111 carcinomas. More than half the cases reported by these authors were in men, whereas most other writers have found the incidence in men

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1. Bruch, Carl: Die Diagnose der bösartigen Geschwülste, Mainz, V. v. Zabern, 1847; quoted by Frazier, C. H.: Sarcoma of the Stomach, Am. J. M. Sc. **147**:781-788 (June) 1914.

2. D'Aunoy, R., and Zoeller, A.: Sarcoma of the Stomach: Report of Four Cases and Review of the Literature, Am. J. Surg. **9**:444-464 (Sept.) 1930.

3. Pack, G. T., and McNeer, G.: Sarcoma of the Stomach: A Report of Nine Cases, Ann. Surg. **101**:1206-1224 (May) 1935.

4. Balfour, D. C., and McCann, J. C.: Sarcoma of the Stomach, Surg., Gynec. & Obst. **50**:948-953 (June) 1930.

and that in women to be approximately equal. The average age was 43 years. In 1920 Douglas [5] reviewed 230 cases of sarcoma of the stomach in which the average age was 41.6 years, a figure considerably lower than that generally accepted for carcinoma.

Ewing [6] divided the sarcomas of the stomach into three distinct types: spindle cell myosarcoma, lymphosarcoma and miscellaneous round cell or alveolar sarcoma. He stated that the spindle cell myosarcoma forms "solid or cystic growths, single or multiple, which project from the wall of the stomach into the peritoneum, or remain interstitial or protrude into the cavity of the organ, where they suffer necrosis and ulceration." He pointed out that in the majority of cases the tumor arises from a curvature rather than from the pylorus. In describing the manner of growth he added that a large sarcoma is often cystic and tends to form bulky metastases in the liver, which likewise frequently become cystic and may even transform the organ into a series of large cystic tumors. He emphasized the fact that the differential diagnosis of spindle cell sarcoma and myosarcoma is frequently difficult and tends to vary with different observers.

Kaufmann,[7] in discussing the site of origin of the lesion in the wall of the stomach, stated that in the great majority of cases the tumor arises in the submucosa or muscularis, a tumor arising from the subserosa or mucosa being rare. He pointed out that a sarcoma which occupies chiefly the inner layers and is of the round cell type may be difficult to differentiate from a round cell carcinoma. However, as an aid to differential diagnosis, he emphasized the fact that these sarcomas "do not select the pylorus so frequently; they are oftener a clinically demonstrable tumor, show less tendency to ulcerate, are less malignant and usually of longer course; sometimes they reach the size of a man's head and a weight up to 12 pounds, which never happens with carcinomas." Kaufmann observed a myosarcoma of the stomach as large as a child's head, with enormous metastatic lesions in the liver. He pointed out that metastases appear in approximately one third of the cases of sarcoma of the stomach, most frequently in the regional lymph nodes and the liver but occasionally in other organs. A histologic classification was given in 100 of the tumors in the 135 cases reviewed by D'Aunoy and Zoeller, as follows: 63 per cent, lymphosarcoma and round cell sarcoma; 14 per cent, fibrosarcoma and spindle cell sarcoma, and 9 per cent, myosarcoma. In Balfour and McCann's group of 54 cases

5. Douglas, J.: Sarcoma of the Stomach, Ann. Surg. **71**:628-638, 1920.

6. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 277.

7. Kaufmann, E.: Pathology, translated by S. P. Reimann, ed. 8, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 690.

there were 45 in which operation was performed and microscopic examinations were reported. The diagnoses in these cases were as follows: lymphosarcoma, 71.3 per cent; fibrosarcoma and spindle cell sarcoma, 13.3 per cent, and myosarcoma, 6.7 per cent. It appears from these observations that the myosarcomas constitute a relatively small group.

Most observers have agreed that sarcoma of the stomach in general is more readily removed at operation and metastasizes later than carcinoma, thus offering a better operative prognosis. Surgical intervention appears to be more remedial for myosarcoma and fibrosarcoma than for lymphosarcoma and small round cell sarcoma.

The detailed report of the case presented is as follows:

REPORT OF A CASE

The patient was a 48 year old American-born housewife. She came to the medical outpatient department of the New York Hospital for the first time on Jan. 22, 1934, complaining of abdominal distention, epigastric distress, belching and abdominal cramps of one and one-half years' duration.

Family History.—The patient's mother died at the age of 49, having had inflammatory rheumatism. She was said to have had psychopathic tendencies for many years. The patient's father died of abscess of the lung at the age of 64. There were no brothers or sisters. The patient's paternal aunt died of tuberculosis, and the patient was exposed to this disease only when on occasional visits. Her maternal uncle was said to have had heart disease. The husband had always been well. The patient had one child, who died of quinsy when 2 months old. There were no other pregnancies. There was no family history of diabetes, cancer, gout or renal disease.

History.—The patient was born in New York and had always lived in the vicinity. She had been married for twenty-one years. The only illnesses which she was able to recall were whooping cough, measles, scarlatina and influenza. Apart from the fact that she worried a great deal about her mother's condition and about financial matters, her general health had been good until the onset of the present illness.

There were no symptoms referable to the head and neck except rather frequent headaches in the supra-orbital region, which started six months before her admission to the clinic. She had not complained of pain in the chest, and only on rare occasions did she have a cold accompanied with a mild cough. No sputum, hemoptysis, asthma or hay fever had been noted. Night sweats were associated only with the present illness, as were precordial pain, heart burn, dyspnea and palpitation. There was never any cyanosis or edema of the ankles. Beginning two years before the patient's admission to the clinic her husband noticed that her face was puffy and swollen on occasions, the condition being most noticeable when she arose in the morning and disappearing during the course of the day. This symptom, however, gradually disappeared. The menstrual cycle commenced when she was 12 or 13 and occurred every twenty-one days, each period lasting for two or three days. The flow was scanty. The last menstrual period was in January 1933. There was never any marked leukorrhea. There were no symptoms referable to the neuromuscular system. She abstained from the use of alcohol,

tobacco, tea and coffee. Her best weight was 145 pounds (66 Kg.) many years before her admission to the clinic. She gradually lost weight over a period of years and attributed this largely to worry. Her average weight in recent years had been 118 pounds (53.5 Kg.). At the time this record was made it was 120 pounds (54.5 Kg).

Present Illness.—In 1929 the patient began having periodic attacks of moderately severe generalized abdominal pain which became localized in the left upper quadrant of the abdomen and persisted for two or three days. There were no associated symptoms until two years before her admission to the clinic, when she had an attack of diarrhea lasting for ten days. There was no evidence of blood in the stools at this time. About September 1932 she noticed while bathing an unusual fulness in the epigastrium. She was advised by her physician to have roentgenograms made. This was done by a chiropractor, and the films were read by her physician, who reported that no abnormality was revealed. After this she had several chiropractic treatments. After each of three of these manipulations the patient fainted. However, she thought that the lump had disappeared. One month later she was again aware of the mass and also of a dull, continuous pain in the left upper quadrant of the abdomen. At first the pain seemed to be relieved somewhat by the ingestion of food. At this time she began having severe abdominal cramps, but her physician is said to have reported that physical examination revealed no abnormality. Shortly after she commenced having abdominal cramps, she began to be troubled a great deal with gas on the stomach, the discomfort being relieved by belching. Meanwhile, the tumor progressively increased in size. A few months before her visit to the hospital she began eliminating various articles from her diet in an attempt to relieve the epigastric distress. As far as she could remember she had vomited only two or three times in her life, and on these occasions there was no evidence of blood in the vomitus. She had always been constipated but had never noticed any tarry, bloody or clay-colored stools. She could not recall that the skin ever had a yellowish tint. Her symptoms became steadily worse after the onset of the present illness. As the tumor became larger she was aware of increasing dyspnea and palpitation on slight exertion, and she complained of heart burn and precordial pain after the ingestion of food. For two or three months before her admission to the clinic she had been having occasional night sweats and had noticed that she was not as strong as she had been formerly.

Physical Examination.—The patient was a thin but fairly well developed white woman, lying comfortably in bed. The skin was clear, and the mucous membranes had a good color. The skull, scalp and hair were normal, and there was no tenderness over the sinuses. The auricular canals and drums were not unusual, and hearing was not impaired. The pupils were equal, and they reacted to light and in accommodation. The external ocular movements were normal. The arteries of the fundus showed slightly increased light reflexes. Examination of the nose revealed no obstruction, discharge or defect of the nasal septum. The teeth and gums were in good condition. The tongue was slightly coated, and the tonsils were small and buried. The pharynx was not injected. There was no stiffness or rigidity of the neck, and no general glandular enlargement was noted. The thyroid gland was not enlarged. The chest was narrow and thin walled. The lungs expanded equally, and the breath sounds were clear throughout. The cardiac apical impulse was weak and diffuse. There were no thrills, and the heart was not enlarged to percussion, the left border being 9 cm. from the midline. The sounds were of good quality, and there were no cardiac murmurs. The radial

arteries were somewhat thickened. The veins in the neck were moderately distended. The blood pressure was 118 systolic and 70 diastolic. The breasts were small and atrophic. No nodules could be palpated.

The abdomen was greatly enlarged and protuberant, and the veins in its upper portion were prominent. There was a large mass filling most of the abdomen in a symmetrical fashion. In some areas this mass felt solid, but in others it felt distinctly cystic. It was not tender. The upper border was continuous with the costal margin across the entire abdomen. The lower border was sharply defined and irregular in contour. It extended across the entire lower portion of the abdomen, well below the level of the umbilicus. The greatest diameter of the tumor was from the xiphoid process to the border of the tumor, a distance of 22 cm. The greatest circumference of the abdomen was 76 cm. The whole mass descended with inspiration. The liver and spleen could not be identified. Below the border of the tumor there was evidence of only a small amount of free fluid within the abdominal cavity. The kidneys were not palpable. On pelvic examination the uterus was of normal size, mobile, retroverted and retroflexed. The adnexa were not felt. There were no palpable masses within the rectum. The reflexes were normal. The extremities were not unusual. There was no edema.

Course.—The patient was advised to enter the hospital for treatment but at this time refused to do so. Between the date of her first visit to the clinic and her admission to the hospital, more than two months later, investigation was continued at the clinic. On Jan. 23, 1934, the blood count showed: erythrocytes, 3,860,000; white blood cells, 9,200, and hemoglobin, 77 per cent. The differential smear showed: adult polymorphonuclears, 49 per cent; immature polymorphonuclears, 8 per cent; monocytes, 5 per cent; lymphocytes, 30 per cent; eosinophils, 5 per cent, and basophils, 3 per cent. On repetition the results were approximately the same. The Kline and Wassermann tests of the blood were negative.

On January 22 a proctoscope was passed for a distance of 25 cm. and revealed no abnormality. This was repeated with the same result on the following day.

On February 16 stool culture for Endamoeba histolytica gave negative results. On February 17 gastric analysis showed 30 degrees free acid and 45 degrees total acid. Roentgen examinations during this period gave the following results: On January 24 a barium sulfate enema showed that the colon was normal. On February 15 the stomach and duodenum were observed to be distorted by extrinsic pressure. The cardiac end of the stomach was compressed by a mass which was thought to be an enlarged spleen. The lower end of the stomach was depressed by a mass which was thought to be the liver. There were no intrinsic filling defects. The six hour examination revealed a small amount of barium retained in the stomach, the head of the barium meal being in the splenic flexure; the twenty-four hour examination showed that the colon was normal. On March 10 a similar examination revealed the same picture. A flat plate of the chest showed that the diaphragm was high, but it was otherwise normal. The hepatic shadow showed no areas of increased or decreased density, and the liver appeared to be diffusely enlarged. On February 7 a cholecystogram failed to show a definite shadow of the gallbladder. The test was repeated on February 25, with a doubled oral dose of the dye, and the result was the same.

On March 27 the patient was prevailed on to enter the medical ward for observation. Since her first visit to the clinic the symptoms had progressed, but she was still able to be up and about. She commenced having mild chills and slight fever on occasions. She was able to take only a small amount of food at a time because of the epigastric distress and fulness which eating produced. The

mass was increasing in size. A film of the chest at this time showed no evidence of a primary growth or metastases. A flat plate of the abdomen revealed a mass occupying most of the upper three fourths of the abdomen and pressing down on the transverse colon. In the lateral view the mass was seen to occupy the anterior position. Films of the lumbar region of the spine and sacrum showed no metastatic lesions. Examination of the urine on one occasion revealed slight albuminuria, with occasional red and white blood cells and no bile. On a second occasion the urine was normal. The red blood cell count varied between 3,200,000 and 4,200,000. There were 10,500 leukocytes, and the hemoglobin value was 63 per cent. The differential smear was normal. The Kline test was repeated and again showed a negative result. The urea nitrogen content of the blood was 10 mg. per hundred cubic centimeters, and the sugar content 87 mg. The icteric index was 15 and 7.5. The van den Bergh test showed negative results. Gastric analysis showed no free hydrochloric acid in the fasting specimen and a maximum of 10 one hour after the ingestion of 30 cc. of 7 per cent alcoholic solution. There was no blood in the specimen. The patient remained in the hospital for a period of ten days, and during this period there was a slight daily elevation of the temperature. The skin showed a questionable subicteroid tint. The patient's condition was variously diagnosed as primary carcinoma of the liver, Banti's disease, cystic kidney and pancreatic tumor. The surgeon, called in consultation, favored the diagnosis of pancreatic cysts and advised laparotomy. However, the patient refused any kind of operation. She was discharged on April 6 and was instructed to return to the clinic in three weeks.

The patient did not report to the clinic, and we were unable to follow the course until she was brought to the accident room on August 18, when she was seen to be in a grave condition. She was immediately admitted to the surgical service. In the interval of four and one-half months the abdominal mass had progressively increased in size and had gradually become painful, especially during the two weeks preceding the patient's admission to the hospital. Her appetite had slowly failed, and she was unable to take more than a small quantity of food at a time. Constipation persisted. There were no tarry, clay-colored or bloody stools or vomiting. The patient had not noted any jaundice. Dyspnea and palpitations became extreme on slight exertion. Weakness was progressive, but she weighed 3 pounds (1.3 Kg.) more than on her first visit to the clinic. Although she was weak, she was able to be up and about most of the time until two weeks before admission to the hospital, when she caught cold and was forced to stay in bed until she was brought into the hospital. During these two weeks there was a persistent elevation of temperature. The physical examination gave the same results as the previous one except for these facts: The general appearance was obviously that of a gravely ill woman. Slight exertion was difficult for her. The abdominal mass had greatly increased in size. The lower border was still clearly defined and irregular in contour. It extended to about 6 cm. above the pubis. Palpation again revealed solid and cystic areas. The mass was not tender. It descended with inspiration. The veins in the upper part of the abdomen were more distended than they had been at the time of the first examination. The skin and scleras showed no icteroid tint.

Examination revealed that the urine was normal. The red blood cell count varied between 3,500,000 and 2,500,000, and the leukocyte count, between 33,500 and 41,500. The differential smear showed that most of the polymorphonuclear leukocytes were of the immature type. Chemical analysis of the blood showed: urea nitrogen, 12 mg. per hundred cubic centimeters; sugar, 60 mg.; calcium, 9

mg., and phosphorus, 3.8 mg. The icteric index was 6. A flat plate of the abdomen revealed the same picture as on the previous occasion, except that the mass had increased in size. A film of the chest showed that the diaphragm on the right side was high. The costophrenic angles on both sides were obscured, but the fields of the lungs were not otherwise unusual. A barium enema corroborated the results of the previous examinations, which showed that the colon was normal. Unfortunately, the patient was too ill for a repetition of the entire gastro-intestinal examination. After admission to the ward the patient failed rapidly. The temperature rose gradually in steplike formation. The second day after her admission to the hospital she was unable to take anything by mouth, and on the fifth day a definite yellowish tint was observed in the skin.

Fig. 1.—Photograph of the gross specimen of leiomyosarcoma of the stomach with massive metastases to the liver.

This steadily deepened. Fluids were administered by infusions and clyses. Weakness became extreme, and on August 26 the temperature rose to 42.5 C. (108.5 F.), and the patient died.

Postmortem Examination.[8]—The body was that of a white woman of the intermediate anatomic type, considerably undernourished. The weight was 116 pounds (52.5 Kg.). The skin and scleras were slightly icteric. There was moderate edema of both lower extremities. Thrombosed external hemorrhoids were present. The peritoneal, pleural and pericardial cavities contained 150, 100 and 75 cc., respectively, of clear, watery yellow liquid. General routine examination revealed no other unusual features.

8. The autopsy was performed by Dr. H. S. Dunning, of the department of general pathology.

Stomach and Liver (see the drawing of the gross specimen, fig. 1): The upper portion of the abdominal cavity was occupied by a huge, roughly oval tumor, measuring 30 cm. in the longitudinal axis of the body, 17 cm. in the transverse axis and 10 cm. in the anteroposterior axis. It lay between the two layers of the lesser omentum between the stomach and the liver. These peritoneal membranes were tightly stretched over its anterior and posterior surfaces. The mass occupied a position over the anterior aspect of the stomach, duodenum and pancreas, which were flattened. It had compressed the left, the caudate and the quadrate lobe of the liver, pushing them forward and upward, thus elevating the diaphragm. The

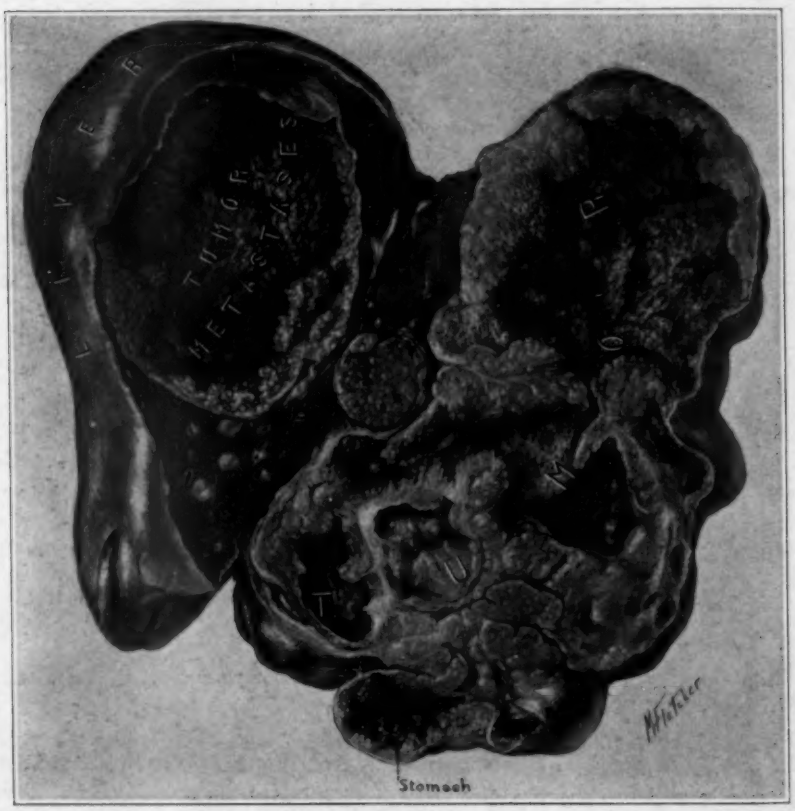

Fig. 2.—Drawing of the gross specimen of leiomyosarcoma of the stomach with massive metastases to the liver

mass was attached to the liver by delicate fibrous adhesions. It had pressed the spleen into the extreme upper left portion of the abdominal cavity and had displaced the transverse colon and the greater omentum downward into the lower portion of the abdomen. The tumor was directly continuous with the wall of the stomach, which it replaced in a round area, 5 cm. in diameter, in the anterior portion of the cardia just below the esophagus. Here the tumor projected slightly into the gastric cavity and was covered only with thin, transparent mucosa, except where the tumor tissue formed the walls of two round ulcers, 1.6 and 0.5 cm. in

their respective diameters. Squeezing the tumor caused the exudation of gray, putrid-smelling, thick liquid, containing shreds of dead tissue, from the inside of the mass through these holes into the gastric cavity. Sectioning showed that the whole center of the tumor was necrotic, thus producing a cystic structure the wall of which was composed of ivory-colored, homogeneous, firm tissue containing numerous hemorrhages. This wall was in some places only 2 cm. in diameter. Numerous round circumscribed masses of the same tissue were embedded in the liver. They varied in diameter from 5 mm. to 12 cm. The largest mass

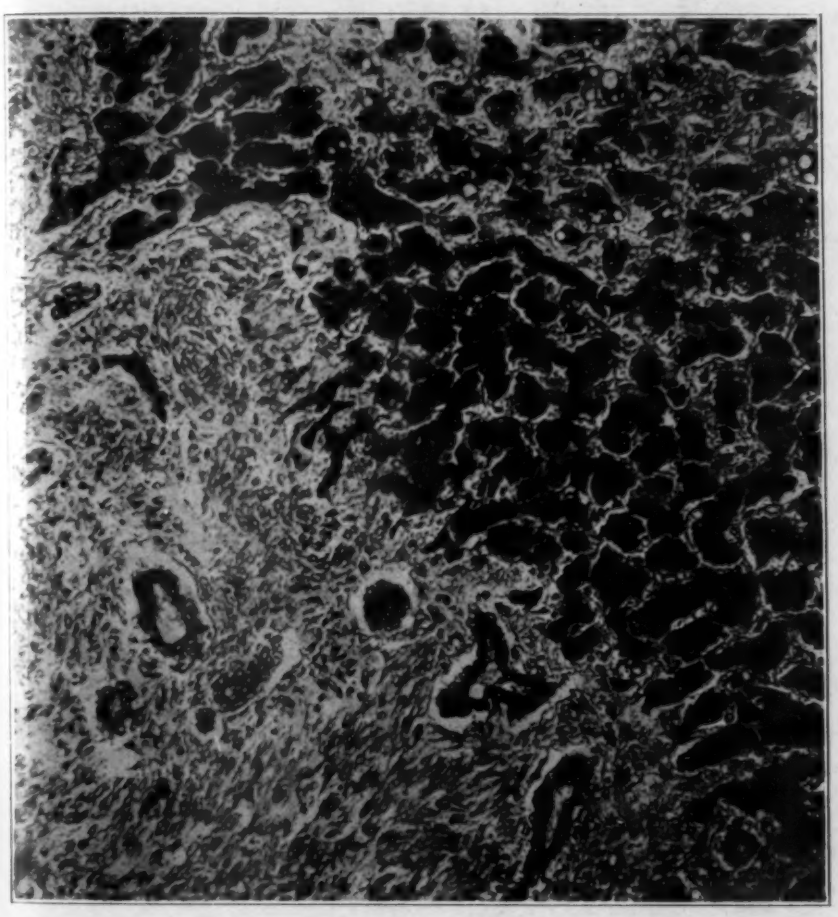

Fig. 3.—Metastasis to the liver. The tumor lies in Glisson's capsule, where it is not encapsulated but fades off into the surrounding parenchyma. Throughout the masses of tumor cells are proliferating bile ducts similar to those seen in cirrhotic processes.

occupied the midportion of the right lobe of the liver and consisted of a shell of tumor substance filled with watery blood and necrotic tissue. The parenchyma of the liver between the tumor nodules was congested. The gallbladder and the cystic, hepatic and common bile ducts, portal vein and hepatic artery were normal. The hepatic, splenic and celiac lymph nodes were normal.

Microscopic examination showed that the primary tumor in the stomach occupied the musculature of the organ, lying in the muscle coats and pushing out the muscularis mucosae and the mucosa before it. The mucosa was necrotic and formed the bed of an ulcer which extended down into the tumor. Large spheroidal masses of tumor cells lay between the ulcer and the serosa and spread out on either side. They were surrounded by thin capsules which seemed to be composed of muscle strands rather than of connective tissue.

Fig. 4.—Photomicrograph of the primary tumor in the stomach.

The metastasis in the liver (fig. 3) lay in Glisson's capsule, where it was not encapsulated but faded off into the surrounding parenchyma. Throughout the masses of tumor cells were proliferating bile ducts similar to those seen in cirrhotic processes.

Microscopic examination [9] of the leiomyosarcoma of the stomach (fig. 4) showed that it was composed of more or less spheroid masses of cells that lay in bundles or leashes. With the hematoxylin and eosin stain the cells showed a rather stout body with processes that extended outward and anastomosed with similar processes

9. Dr. Nathan Chandler Foot made the microscopic study of the tumor.

from neighboring cells, the cytoplasmic material forming a vacuolated network of intercellular bridges. This was reminiscent of the appearance of embryonal smooth muscle. The cytoplasm was acidophilic, pink with eosin, red with Mallory's connective tissue stain and with Masson's trichrome process and reddish yellow in phosphotungstic acid and hematoxylin preparations. The nuclei were hyperchromatic and elliptic, with gently rounded poles like those of smooth muscle cells, not tapering and pointed like those of fibroblasts. Mitotic figures were not seen, in spite of prolonged searching. Tumor giant cells that exactly resembled the type cell but were about twice its size were occasionally present. The stroma was composed of collagenous tissue and was not copious. Instead of running around and between the cells, as it would in the case of the matrix of a fibrosarcoma, it tended to outline the cell bundles like a sheath. This was only occasionally well developed, and there were areas where the connective tissue had become massed into scarlike septums and partitions in the tumor. This was particularly true of the unit masses already described, and these were surrounded with connective tissue sheaths or capsules that were thin and often broken through.

Diagnosis.—From the arrangement of the cells, the location of the tumor in the musculature of the stomach, the presence of gently rounded elliptic nuclei and the tendency of the cells to anastomose and form a cytoplasmic reticular syncytium, one may deduce that this was a leiomyosarcoma rather than a fibrosarcoma. This assumption is further strengthened by the great scarcity of mitotic figures, which is a rather commonly encountered phenomenon in a leiomyosarcoma and unusual in a rapidly growing fibrosarcoma.

COMMENT

The outstanding clinical features of this case are as follows: (1) the absence of vomiting, (2) the lack of evidence of bleeding into the gastro-intestinal tract, (3) the failure to demonstrate by roentgen examination a filling defect in the stomach, (4) the absence of appreciable jaundice until two days before death and (5) the fact that the patient gained 3 pounds (1.3 Kg.) in weight during the terminal seven months of the illness.

These circumstances, which must be considered unusual in connection with a gastric lesion, may be explained in the following manner: 1. The tumor involved only a small area of the gastric wall and projected mainly outside the stomach; therefore there were no symptoms of obstruction. 2. The mucosa of the stomach was little involved; therefore, there was no demonstrable bleeding into the gastro-intestinal tract. 3. Not only was the mucosa little involved, but the cavity of the stomach was not deformed by a mass, so that no actual filling defect was shown roentgenographically. 4. In spite of the extensive replacement of hepatic tissue by tumor, there remained, it must be assumed, sufficient hepatic substance to prevent the development of jaundice until the absorption of necrotic, infected primary and metastatic growth caused symptoms of toxemia. 5. The gain in weight in a patient who was

apparently moribund was explained at autopsy by the presence of a large amount of fluid in the peritoneal cavity and by the weight of the primary and secondary tumors.

CONCLUSION

A case of leiomyosarcoma of the stomach in an advanced stage is described, with full clinical and autopsy reports. When one is confronted with an epigastric tumor, even in the absence of obstruction, without demonstrable filling defects on roentgen examination and without bleeding into the gastro-intestinal tract, it is important to bear in mind the possibility of sarcoma of the stomach, particularly if the patient is in the fourth or fifth decade of life.

A NEW TEST FOR EVALUATING CIRCULATION IN THE VENOUS SYSTEM OF THE LOWER EXTREMITY AFFECTED BY VARICOSITIES

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It has been forty-five years since Trendelenburg [1] (1891) reemphasized the most important factor concerned in the disturbance in function of varicose veins of the lower extremity. In this paper he demonstrated incompetence of the valves of the internal saphenous vein and the reversal of circulation that results, i. e., the peripheral flow of blood to the superficial venous system. Moreover, he popularized an operation [2] which is the most direct attack on the physiopathologic factor, namely, ligation and section of the long saphenous vein to prevent the blood from spilling from above through the saphenous vein into the varicosities. The good results he obtained with this operation in a large series of cases were later reported by Perthes.[3] Since that time much has been added to the knowledge of individual methods and combinations of methods for the treatment of varicose veins, and the problem has been shown to be not so simple or easy of solution as perhaps appeared to Trendelenburg and Perthes. The trends and changes in the methods of managing varicose veins have been numerous, and today the question as to the best method is by no means settled; the last chapter has not been written. Sometimes fatalities, but usually recurrences—disappointments that followed in the wake of each enthusiastically received new method of management—resulted in further search for a safe, simple way of permanently curing varicose veins. So far none has proved to be satisfactory, though undoubtedly today the surgeons most skilful in the knowledge and technic of the best procedure indi-

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1. Trendelenburg, F.: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvaricen, Beitr. z. klin. Chir. **7**:195, 1891.

2. According to Trendelenburg, others, including Ambroise Paré, had ligated the internal saphenous vein for relief from varicosities.

3. Perthes, Georg: Ueber die Operation der Unterschenkelvaricen nach Trendelenburg, Deutsche med. Wchnschr. **1**:253, 1895.

cated in the individual case secure better and more lasting results than have most workers in the past. Only to the inexperienced will this particular phase of the practice of the art of healing seem simple and easy and without the amenities of study-stimulating complexity and its at least intellectual recompense.

So many variable factors are active in the production of varicose veins that a number of different types or patterns require individual methods of management. In order to treat intelligently a patient with varicosities of the lower extremity a survey by certain tests is necessary to evaluate the condition of the circulation in the superficial and deep veins and in the communicating veins. In the surgical clinic of the Tulane University School of Medicine we employ as a routine the tests to be described, and sometimes others less helpful, in every case of varicose veins of the lower extremity before outlining the plan of treatment. One of these methods (described last) is a test which we developed and the information it furnishes is important in planning the proper management of the particular condition and in predicting the dangers of recurrence.

TESTS FOR EVALUATION OF CIRCULATION IN VARICOSE VEINS

1. *Trendelenburg Test.*—This test was adequately described [4] forty-five years before the appearance of the paper by Trendelenburg. It is applied thus: The patient reclines on a table. One leg is elevated to the vertical position and is supported in this position for a few minutes in order to empty the superficial veins. The leg is lowered to the dependent position, and the patient rises to the sitting and then to the standing position. The varicosities distend quickly if the valves of the internal saphenous vein are incompetent, owing to the unresisted rush of blood from the femoral vein through the saphenous veins. The patient again assumes the reclining position, and the leg is elevated. The fingers of the observer are placed over the upper end of the vena saphena magna, and firm pressure is applied. The leg is lowered to the horizontal position, and the patient swings around and stands on the floor while the fingers are still so firmly applied that they prevent movement of

4. The method was described by Sir Benjamin Brodie (Lectures Illustrative of Various Subjects in Pathology and Surgery, London, Longmans, 1846, vol. 7) as follows: "If I put on a bandage and squeezed the blood out of the veins below and then put my thumb on the vena saphena above so as to stop the circulation through it, I found on taking off the bandage, the patient being in the erect posture, that the cluster of veins below filled very slowly and only from the capillary vessels; but if the patient be in the erect position, I removed the pressure from the veins, the valves being of no use the blood rushed downward by its own weight contrary to the course of the circulation and filled the varicose cluster below almost instantly."

the blood through that segment of the vein. As soon as the patient is in the erect position the observer fixes his attention on the degree of prominence shown by the veins of the calf and lower part of the thigh. If the pressure is maintained, the varicose veins fill slowly from below. When the pressure on the saphenous veins is suddenly released the rapidity with which the varicosities fill is noticed. If the veins suddenly fill and bulge as though the blood has been dumped into them, it indicates incompetency of the valves of the long saphenous vein. Later, a further evolution of this test came to be known, the source of which is obscure. If the pressure on the saphenous vein is maintained and the varicosities fill rapidly—more rapidly than might be expected to occur through the capillaries alone (which takes about thirty-five seconds)—the interpretation is made that the varicose veins fill from incompetent collaterals below the point of pressure (fig. 1). Thus, when the Trendelenburg test shows incompetence of the saphenous valves and the secondary test more rapid filling than usual, indicating incompetence of the valves of the communicating veins, the reaction to the Trendelenburg test is said to be doubly positive.

A doubly positive Trendelenburg reaction is of significance. It indicates retrograde flow from the deep to the superficial system, not only through the main entrance of the long saphenous vein into the femoral vein but through the communicating channels below between the deep and the superficial system. Prior to development of the test to be described later there was no accurate way of determining whether the communicating veins with incompetent valves were in the thigh or calf or both. In an excellent paper published in 1910 Moro [5] stated that incompetency of the valves of the communicating veins is not always diagnosed clinically. He found that the Trendelenburg operation failed to effect cure in 55 per cent of the cases in his series and expressed the belief that the failure was due to incompetency of the valves of the communicating veins, which he attempted to remedy by further surgical procedure. His criterion for incompetency of the valves of the communicating veins was only a postoperative observation, viz., that ligation of the internal saphenous vein did not cure the condition in certain of his cases (55 per cent), resulting in little if any improvement in the condition in these instances. Homans [6] in 1916 expressed greater appreciation of the method for preoperative diagnosis of incompetence of the valves of the communicating veins on the basis of the doubly positive reaction to the Trendelenburg test. Since that time authors

5. Moro, G.: Ueber die Pathogenese und die zweckmässigste Behandlung der Krampfadern der unteren Extremitäten, Beitr. z. klin. Chir. **71**:420, 1910.

6. Homans, J.: The Operative Treatment of Varicose Veins and Ulcers Based on a Classification of These Lesions, Surg., Gynec. & Obst. **22**:143, 1916.

have been aware of this way of determining incompetence of communicating veins below the opening of the saphenous vein.

2. *Perthes' Test.*—Perthes called attention to the fact that benefit is to be derived from ligation and section of the long saphenous vein in the cases in which diminution in the size of the varicose veins is shown when the patient walks with a tourniquet around the thigh or with pressure applied by the patient's fingers over the long saphenous vein sufficient to compress it. The test is applied thus: With the patient standing, a rubber tourniquet is tied securely around the thigh sufficiently tight to obstruct the flow of blood in the superficial venous sys-

Fig. 1.—Drawings illustrating a doubly positive reaction to the Trendelenburg test. Although the examiner's fingers still compress the upper end of the long saphenous vein, the varicosities become engorged quickly (in less than thirty-five seconds) by retrograde flow through the communicating veins with incompetent valves (*b*) (from Ochsner, A.: Diseases of the Veins, in Lewis, Dean, and others: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12).

tem. The patient is instructed to walk. If the superficial venous system becomes less prominent under these conditions than when the patient walks without a tourniquet, it indicates that ligation would interfere with retrograde flow of blood through the long saphenous vein and that the patient would be benefited by ligation.

3. *Test for Competency of Deep Veins.*—A bandage, from 3 to 4 inches (7 to 10 cm.) in width, is applied like a puttee to the leg, suffi-

ciently tight to collapse the superficial veins. The patient walks up and down a room or hall for thirty minutes (fig. 2). Freedom from cramp during this period indicates free return of blood through deep veins. Sharp cramps indicate acute passive congestion due to blood which can return neither through the superficial veins because of compression nor through the deep vein because of a preexisting pathologic condition, e. g., an occlusion due to thrombophlebitis. The execution of this test is more difficult than that of the others. The bandage should be sufficiently tight to compress the superficial veins. However, if it is tight enough to compress the muscles also the compression of the muscles in itself

Fig. 2.—Drawings illustrating a test to determine the competency of deep veins. A firm bandage is applied to the leg from the foot to the lower part of the thigh in order to obliterate all superficial veins. The patient walks for thirty minutes. Cramping and discomfort indicate obstruction of the deep veins or of the communicating veins between the deep and the superficial system or of both (from Ochsner, A.: Diseases of the Veins, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12).

interferes with circulation and thus causes cramps and leads to a false interpretation. The test fulfils a need met by none of the other tests. Theoretically it can detect a localized, segmental obstruction in deep veins below the knee, which might not be demonstrated by the Perthes test. In cases, however, in which there is obstruction of the deep veins of the thigh compression of the long saphenous vein in the thigh by a tourniquet (Perthes' test) demonstrates the obstruction by increasing

the size of the superficial veins below. In these cases the Perthes test gives the same information as the test described in this paragraph, for the superficial veins do not collapse when the superficial circulation is obstructed in the thigh by a tourniquet and the patient is walking if the deep veins do not drain the superficial system. The one exception to the rule that the information furnished by the Perthes test is given by this test is in instances in which obstruction of the deep circulation necessitates shunting of the blood through the superficial circulation but the blood returns to a patent deep circulation below the level of the tourniquet (fig. 3).

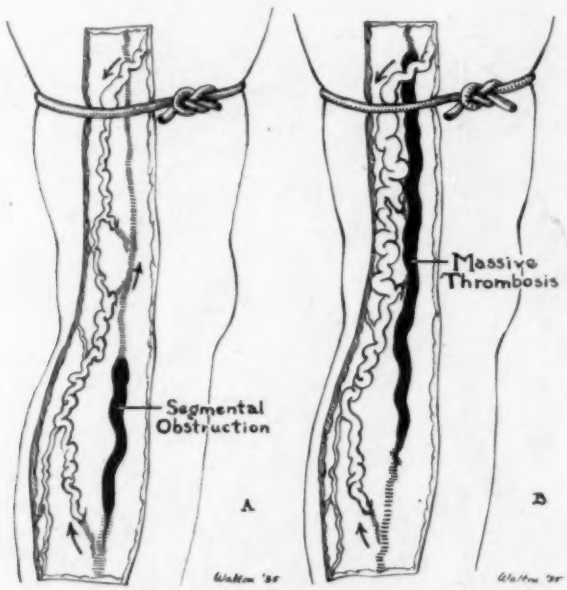

Fig. 3.—Diagrammatic representation of segmental obstruction of the deep veins of the calf. On walking with the tourniquet applied to the thigh (Perthes' test), varicosities below the tourniquet become less prominent because the blood is shunted from the deep system below the obstruction into the superficial system and back into the deep system below the tourniquet. (*B*) Diagrammatic representation of massive thrombosis of the deep veins. In this condition the blood from the extremity can return only through the superficial system and not through the deep veins below the tourniquet, and therefore the superficial system becomes more engorged than when the tourniquet is not applied. In an instance of this condition the Perthes test discloses the obstruction to the deep venous system as well as the test illustrated in figure 2, in contrast to the results in instances of segmental obstruction of the deep veins (*A*). On walking, the varicosities below the tourniquet become more prominent.

The most frequent cause of thrombosis of the deep veins of the lower extremity is pelvic infection, and in instances of such thrombosis the

femoral veins are principally involved. In relatively exceptional cases, however, thrombosis of the deep veins of the leg without concomitant involvement of the deep veins of the thigh occurs, and in such instances the test described here is of value because obliteration of the dilated superficial veins of the leg is ruled out.

Our Test.—We devised this test in the Tulane University surgical clinic: The patient disrobes sufficiently to show the thighs and legs. The degree of prominence of the varicose veins on standing is noted by the observer. It is essential to have a good light placed behind the sitting observer and directed toward the area of the room immediately in front of him. It is also important for the observer to sit on a low chair or stool so that his horizontal plane of vision is not much higher than the hips of the patient, permitting good views of the lower extremities. The patient then walks to and fro in front of the observer, who carefully notes any changes in the size of the veins as compared with their size in the standing position. Usually as the patient walks the veins become less prominent, owing to efficient pumping action by the muscles on the deep veins (fig. 4 *a*). After the patient has passed in review several times in this fashion, a tourniquet of thin rubber tubing is tied around the upper third of the thigh, sufficiently tight to compress the superficial veins (fig. 4 *b*). The patient then walks at the same rate of speed over the same course as before, and the observer notes the relative size of the veins as compared with their size when the patient walks without the tourniquet. Usually there is marked diminution in the prominence of the varicosities, the appreciable reduction being from 50 to 75 per cent of the degree of prominence of the veins when the patient walks without a tourniquet. This reduction is due to the fact that the circulation in the superficial system at the level of the tourniquet is inhibited and blood cannot flow backward from the femoral vein through the long saphenous vein past this level. The action of the muscles on the deep veins in walking pumps the blood more efficiently toward the heart and, in reality, milks the superficial system free from its contents below the tourniquet, and the veins become less prominent on the surface. The patient stops walking, and the tourniquet is removed and reapplied in the middle third of the thigh (fig. 4 *c*), again sufficiently tight to obstruct the flow of blood in the superficial veins. The patient again walks, and the prominence of the veins in the leg is compared with their appearance when the patient walks without the tourniquet and with the tourniquet applied around the upper third of the thigh. Similarly, the patient walks with the tourniquet around the lower third of the thigh (fig. 4 *d*). Frequently one observes that when the improvement in appearance is only moderate with the tourniquet around the upper third of the thigh, it

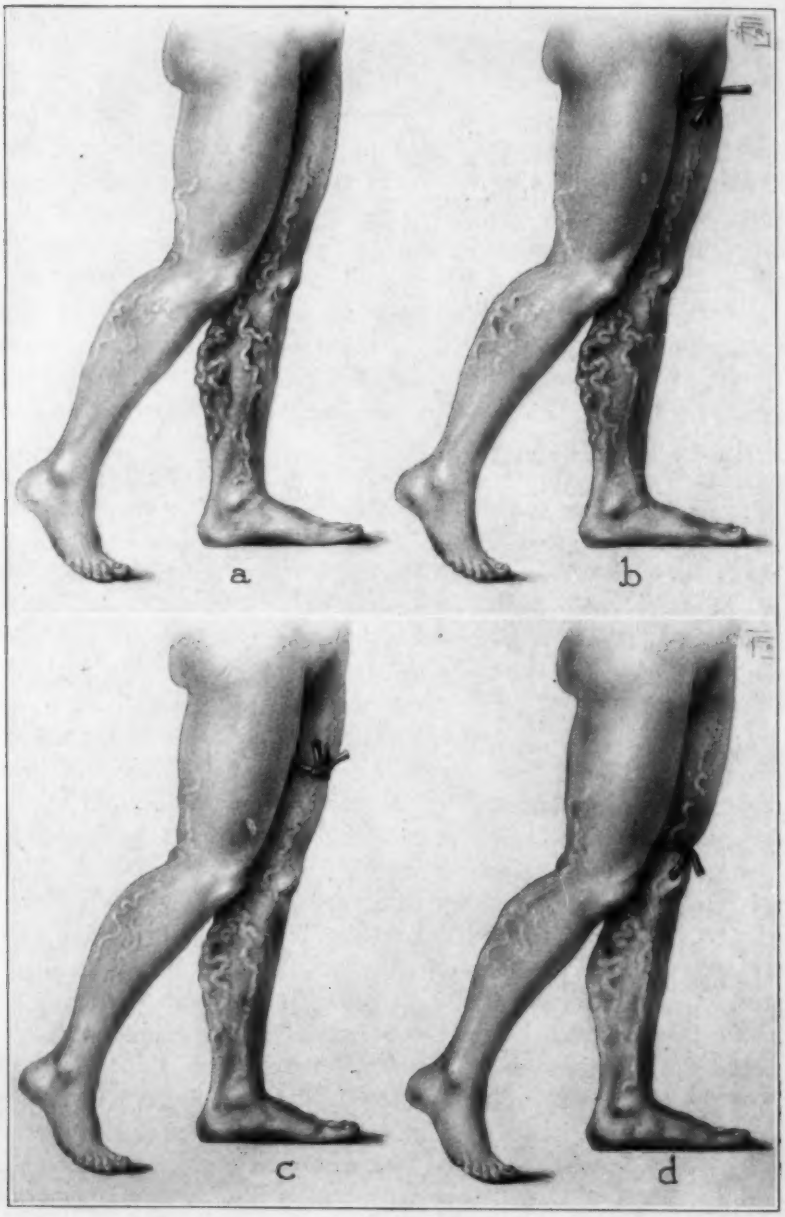

Figure 4

EXPLANATION OF FIGURE 4

Fig. 4—Drawings illustrating the tourniquet test for determining the competency of the valves of the communicating veins between the deep and the superficial system of the thigh. The patient walks at a normal gait, and the prominence of the veins of the calf is noted (*a*). Thereafter the tourniquet is applied to the upper third of the thigh (*b*), sufficiently tight to compress the superficial veins. Observations are made for changes in the appearance of the veins of the calf. At other times the tourniquet is similarly applied to the middle and the lower third of the thigh (*c* and *d*). The patient walks over the same course, and the prominence of the veins is noted. If the valves of all the deep communicating veins of the thigh are competent and the result of the Trendelenburg test is positive there is diminished prominence of the veins of the calf when the patient walks with the tourniquet around the upper third of the thigh. If the valves of the communicating veins are incompetent there is little or no change because the blood spills through the incompetent communicating veins from the femoral to the long saphenous vein. When the tourniquet is below the lowest communicating vein of the thigh in which the valves are incompetent (*d*) the veins of the calf become less prominent. In this instance high ligation alone is not sufficient, and low ligation also must be performed to prevent retrograde flow through communicating veins. In *b* slight improvement is shown over that indicated in *a*, in a case in which the blood spills through the communicating veins below the level of the tourniquet. In *c* slight improvement (diminution in prominence) in the veins of the calf is shown, and in *d* the greatest improvement appears. If the improvement shown in *b* were as great as that illustrated in *d* the test would indicate competency of the communicating veins of the thigh.

is marked when the tourniquet is around the lower third. Thus, the veins of the leg are observed with the patient under five conditions: (1) standing still, (2) walking without the tourniquet, (3) walking with the tourniquet applied around the upper third of the thigh, (4) walking with the tourniquet around the middle third of the thigh and (5) walking with the tourniquet around the lower third of the thigh.

RESULTS OF THE COMPARATIVE TEST

In some instances the veins appear less prominent with the tourniquet on the lower third of the thigh than under any of the other conditions; in other cases there is as much improvement from application of the tourniquet in the upper third of the leg as in the lower third. If the reaction to the Trendelenburg test is positive and the deep veins are not obstructed the varicose veins are less prominent when the patient walks than when he stands still, and they are even less prominent when the tourniquet is applied at each of the three levels of the leg. Usually when the tourniquet is around the lower third of the thigh the varicosities are less prominent than under any other of the five conditions. This is diagrammatically represented in figure 4 *a*, *b*, *c* and *d*, drawn from the appearance in an actual case. As shown in the drawings, the greatest improvement occurred when the tourniquet was around the lower third of the thigh.

In general, this test may have three results: (1) A frequent observation (40 per cent of the instances) is that improvement is greatest when the patient walks with the tourniquet around the lower third of the thigh and less when the tourniquet is around the middle or the upper third of the thigh but that even then it is more marked than when the patient is walking without the tourniquet; (2) the most frequent finding is that there is no difference in the size of the veins when the tourniquet is in any one of the three positions and that yet there is definitely more improvement when the tourniquet is around the thigh than when it is not, and (3) the least frequent finding is that there is no improvement with the tourniquet or that the veins are more prominent when the tourniquet is around the thigh than when it is not.

INTERPRETATION OF THE COMPARATIVE TEST

In instances in which the greatest improvement is seen when the tourniquet is around the lower third of the thigh, some variable must account for the fact that the improvement is greater under this condition than when the tourniquet is around the upper third of the thigh. This further improvement indicates not only that the retrograde flow through the saphenous vein comes through the main opening into the femoral vein but that there is a backward flow below the highest application

of the tourniquet which is caught when the tourniquet is moved lower. This backward flow is undoubtedly through incompetent communicating veins between the superficial and the deep system of the thigh. This is diagrammatically shown in figure 5. In the first instance, illustrated in figure 5 *d*, the tourniquet is placed above the incompetent communicating vein, and the superficial veins of the calf are still distended because the blood spills through the communicating vein to fill the veins of the calf. In figure 5 *c* the tourniquet is shown below the incompetent communicating vein, and the veins of the calf are collapsed. In this case the blood in the superficial system drains into the deep system below the tourniquet, which drainage is facilitated by the pumping action

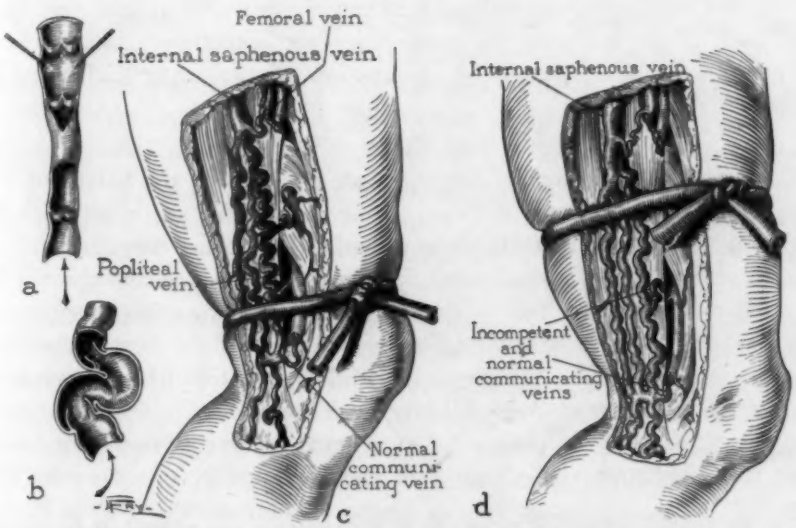

Fig. 5.—Diagrammatic representation of the mechanism involved in our test for determining the competency of the valves of the communicating veins between the superficial and the deep system of the thigh. The valves of the communicating veins above the tourniquet are incompetent (*b*) and those below are competent (*a*), thus not permitting the blood to flow from the femoral to the internal saphenous vein below the tourniquet. When the patient walks with the tourniquet as in *c*, the prominence of the veins of the calf diminishes. As compared with the positions shown in figure 5 *a*, *b* and *c*, *d* illustrates the tourniquet above the communicating veins with incompetent valves. The blood spills from the femoral vein into the internal saphenous vein through the communicating veins, and when the patient walks the change in the appearance of the veins of the calf is not as pronounced as when the tourniquet is below the communicating veins with incompetent valves, as explained in the text.

of the muscles on the deep veins, and the blood can no longer spill from above through the saphenous vein into the superficial veins of the calf.

In the instance in which there is improvement on walking with the tourniquet placed around the thigh but no difference in the degree of improvement whether the tourniquet is high or low, the following conditions are indicated: The valves of the internal saphenous vein are incompetent and there is spillage of blood from the femoral vein through the main opening of the saphenous vein, but the valves of the veins communicating between the saphenous and the femoral vein below the highest level of the tourniquet are competent and there is no retrograde flow at this point from the deep to the superficial system.

Greater prominence of the veins with the tourniquet in place indicates that in spite of the varicosities the blood can return cephalad through the superficial system only and that there is a block in the deep veins or in the veins communicating between the superficial and the deep system. In this instance the varicosities are sometimes spoken of as compensatory, and ligation or obstruction of the superficial veins is contraindicated.

SIGNIFICANCE OF THE TEST

It seems that if there is incompetence not only of the valves of the long saphenous vein but of those of the communicating veins between the long saphenous and the femoral vein, the lower the ligation [7] in the thigh the more improvement in the condition can be expected in the veins of the calf. This is true as far as temporary improvement is concerned; i. e., low ligation in many cases gives the best immediate results, but one cannot ignore the careful observation of such workers in this field as Homans,[8] de Takáts,[9] de Takáts and Quillin,[10] Faxon [11] and Edwards,[12] who emphasized that to avoid recurrence one must interrupt the saphenous vein above its tributaries just before it enters the

7. By ligation we do not mean that ligation alone is our method of treatment. We always use injection in conjunction with ligation in the cases in which we elect to ligate the saphenous vein. Moreover, sometimes we ligate veins other than the main stem of the saphenous vein. The present discussion is limited to indications arising from the test. Ligation means section and ligation of the distal and proximal segments.

8. Homans, J.: The Operative Treatment of Varicose Veins, Varicose Ulcers, and Phlebitis, New England J. Med. **200**:965, 1929; footnote 6.

9. de Takáts, G.: Ambulatory Ligation of the Saphenous Vein, J. A. M. A. **94**:1194 (April 19) 1930.

10. De Takáts, G., and Quillin, L.: Ligation of the Saphenous Vein: A Report on Two Hundred Ambulatory Operations, Arch. Surg. **26**:72 (Jan.) 1933.

11. Faxon, H. H.: Treatment of Varicosities: Preliminary High Ligation of the Internal Saphenous Vein with the Injection of Sclerosing Solutions, Arch. Surg. **29**:794 (Nov.) 1934.

12. Edwards, E. A.: The Treatment of Varicose Veins, Surg., Gynec. & Obst. **59**:916, 1934.

femoral vein. This has been our experience. Moreover, low ligation does not cure the varicosities in the saphenous stem above the level of the ligation. As a matter of fact, low ligation is followed by improvement in the varicose condition not only below but above the level of the ligation, due perhaps to the fact that there is less circulation through the vein above the ligation. We have seen this in a number of clinical cases in which we ligated the long saphenous vein low in the thigh as a first step in the treatment. The fact remains, however, that varicosities tend to recur. Collaterals which are extremely small at the time of ligation may become more active and enlarge and in time become noteworthy stems assuming the function of the saphenous vein that has been tied off. They too may become incompetent. If these collaterals are superficial veins between the proximal and the distal portion of the long saphenous vein one can obviate their incompetence by ligating the internal saphenous vein above all its tributaries. But if in the first place one ligates the saphenous vein just before it empties into the femoral vein there may be retrograde flow through communicating veins below that level, and one may not obtain the benefit of completely interrupting the retrograde flow through the saphenous vein into the veins of the calf. Injection of sclerosing solutions into the distal segment at the time of high ligation may partially or completely prevent this retrograde flow through the communicating veins, but this, too, has its uncertainties. It is not feasible to ligate each communicating stem, even though such a procedure has been advocated by authorities in this field. Search for incompetent communicating stems converts the operation into a major procedure, assuming the proportions of complete extirpation of the internal saphenous vein, and it is unnecessary here to consider the reasons why the last-mentioned operation has been discarded. In the instances in which our test shows the greatest improvement when the tourniquet is around the lowest third of the thigh, we now ligate high to prevent recurrence, inject sclerosing solution into the distal segment at the time of ligation and subsequently ligate lower to obtain the benefit of complete interruption of the flow in the long saphenous vein, even of that through incompetent communicating veins below the main opening of the saphenous into the femoral vein.

There are two observations concerning the value of which we are convinced: (1) If the test we describe shows that the communicating veins between the superficial and the deep system are markedly incompetent and high ligation is made, the patient is somewhat benefited, but little more than if a sclerosing solution were injected into the veins of the calf without ligation, and (2) in instances in which this condition exists low ligation gives by far the greatest immediate improvement. Because, as many authorities maintain, fewer recurrences through col-

lateral veins follow high ligation, in addition to this procedure low ligation may be made for optimum effect and to prevent recurrence through communicating veins.

SUMMARY

A new test is described for determining the direction of flow of blood in the venous system of the lower extremity affected by varicosities and for determining the competency of the valves of the long saphenous vein and communicating veins between the superficial and the deep systems of the thigh. The test gives valuable information concerning the best type of therapy and the possibilities of recurrence.

THE PROBLEM OF WOUND HEALING

I. EFFECT OF LOCAL AGENTS

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PHILADELPHIA

The surgical literature contains reports of the use of numerous topical substances purported to stimulate wound healing. It is my purpose in this article to consider the problem of their evaluation and to present the results obtained in a critical study of certain agents frequently used as wound dressings.

HISTORICAL SURVEY

The Edwin Smith Surgical Papyrus, the first written record in medical history and perhaps the earliest exegesis of the scientific method in human history, contains a discussion of the principles to be followed in the management of traumatic wounds. During the centuries, knowledge has accrued concerning both the mechanisms of repair and the therapeutics of wounds; yet today these subjects remain in the forefront of surgical thought as problems lacking final solution. The fact that surgeons have yet to attain perfection in the treatment of wounds apparently has constituted a challenge to investigators, judging from the multiplicity of substances brought forward to speed up repair. In evaluating these agents one must consider the processses of wound healing, since in the last analysis any substance of worth in wound therapy must act on these functions.

Recognition of the grosser phenomena relating to tissue repair occurred at an early date. The writings of Hippocrates reveal that the Greeks had already distinguished between primary and secondary healing, and Celsus in the first century A. D. attempted to secure the former through the use of sutures, control of bleeding and prevention of pus formation. These measures were discarded during the Middle Ages, with the acceptance of the antithetic Arabian creed that wounds must suppurate to heal. It remained for the surgical leaders of the Renaissance, Hugh of Luccia, Henri de Mondeville and Theodoricus, to restore the concept that healing per primam intentionem is normal and desirable. By the sixteenth century there developed a conflict which remains

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This work was made possible by a contribution from Eli Lilly & Co.

From the Harrison Department of Surgical Research, University of Pennsylvania, and the Surgical Clinic of the Hospital of the University of Pennsylvania.

unsettled to this day. Paré and Paracelsus attributed healing to the inherent forces of nature rather than to the efforts of the surgeon and contended that it is the surgeon's prime duty to permit these forces to act with a minimum of interference. In an opposite school of thought the attitude prevailed that adequate treatment of a wound demands relentless anointment with one vulnerary after another, in order to achieve a maximum rate of healing.

Understanding of the histologic phenomena of repair followed the discovery of the microscope, the enunciation of the cell doctrine and the introduction of the technic for preparing microscopic sections. After Virchow had built his cellular pathology, repair came to be expressed in terms of cellular and vascular reactions. Observation of living tissues by von Recklinghausen and Cohnheim and studies of cultures in vitro clarified the interrelationships among the several cell types—vascular elements, fixed tissue cells and mobile tissue cells—which enter into wound healing.

Concomitantly the influence of bacterial agents on the reparative functions was elucidated. From these developments, which are largely contributions of the past half-century, there has come the present concept of the histology of inflammation and repair, a concept which with respect to its broad outline enjoys general acceptance.

The standard surgical textbooks divide the reactions of the tissue in a traumatic wound into an exudative and a reparative phase. Any irritant destructive of tissue invokes vascular changes and an exudative response of leukocytic and mobile tissue cells and of antibody constituents of the serum, which collectively localize and minimize the effects of the irritant. Reparative phenomena then follow; in surface wounds these consist of capillary budding, fibroblastic proliferation and epithelial ingrowth, all so regulated as ultimately to restore the continuity of the tissue. Harvey [1] has well summarized the events of repair in his statement: "From the view-point of the surgeon, then, the healing of a wound is largely a function of the covering epithelium and certain fibroblastic elements derived from mesenchyme . . ."

While the essential features of the structural mechanism of repair have been established, the underlying forces which motivate the process remain to a large degree obscure. What are the factors consequent on trauma which cause adult cells to resume embryonal proliferative characteristics? After many studies on tissues in vitro Carrel [2] concluded that "healing is not initiated by traumatism or the loss of tissues, but by substances resulting directly or indirectly from the traumatism." He expressed the belief that these growth-promoting substances are protein

1. Harvey, S. C.: Proc. Inst. Med. Chicago **10**:70, 1934.
2. Carrel, A.: Proc. Inst. Med. Chicago **8**:62, 1930.

and that they are liberated either by the breakdown of the tissue itself or by the manufacturing activity of leukocytes, particularly lymphocytes, on cellular débris and the constituents of serum. Fisher [3] resected a triangular segment from a slowly growing culture of fibroblasts and observed a renewal of growth throughout the colony. Subsequent to experiments on plants and animals, Hammett and Reimann [4] advanced the hypothesis that the "sulphydryl group is the wound hormone or essential chemical factor in the cell proliferation following trauma." Whatever the chemical agent which initiates the reparative functions, the more recent tendency has been to seek such a substance rather than to follow the older belief of Virchow that trauma per se activates the cells involved in healing.

No attempt has been made to review all the contributions dealing with the responses of the tissue to injury. Rather I have sought to survey briefly the present knowledge of the processes of repair, because from the point of view of therapeutics a consideration of these processes must serve as a background for the evaluation of the effect of any purported vulnerary. The immediate question confronting the surgeon is whether or not means are available to act on the reparative mechanism in a stimulating manner. Without consideration of forces inherent in a wound it is apparent that the rate of healing may be affected by factors localized directly at the site of the wound and by factors of a more general nature present or administered at a distance.

Variables which may influence healing from a distance are (1) diet, (2) hormones and (3) infection existing elsewhere in the body. From measurements of surface wounds in dogs Clark [5] found that as compared with diets high in carbohydrates and mixed diets, those high in protein shortened the period of latency before healing commenced and those high in fat lengthened it, but that subsequent to its onset repair was not influenced by the diet. On the other hand, observations by Harvey and his colleagues [6] on increasing increments in the tensile strength of gastric incision wounds indicated that diet did not affect the duration of the period of latency but that a diet with a high protein content resulted in more rapid attainment of maximum strength. It was further noted that starvation effected no change either in the rate of incidence of fibroplasia or in its velocity. As a result of these studies Harvey [1] concluded that "the normal animal when subjected to a wound

3. Fisher, A.: Tissue Culture, Copenhagen, Levin & Munksgaard, 1925.

4. Reimann, S. P.: Proliferation of Rat and Mouse Epithelium from Sulphydryl, Protoplasma **10**:82 (June) 1930.

5. Clark, A. H.: Bull. Johns Hopkins Hosp. **30**:117, 1919.

6. Harvey, S. C., and Howes, E. L.: Ann. Surg. **91**:641, 1930.

will repair this without respect to the character of diet or even lack of food . . ." With regard to accessory food factors, investigation has largely centered about vitamin A. Lohr [7] and Continental observers have stressed the beneficial influence of cod liver oil, but Roegholt [8] reported that deficiency of vitamin A caused no alteration in the rate of wound healing. The belief was expressed by Bird and MacKay [9] that patients postoperatively should be placed on high fluid intakes, since moderate dehydration in rats comparable to states observed clinically markedly inhibited the process of repair.

The endocrine glands the functions of which have been correlated with the reparative processes are the pancreas, the thyroid gland, the adrenal glands and the gonads. Rabinowitch [10] cited reports of twenty cases in which the patients did not have diabetes but had a condition marked by impairment in tolerance for carbohydrates, the administration of insulin being followed by rapid closure of a previously nonhealing wound. Sullivan [11] obtained a similar response with postpellagrous trophic ulcers. On the basis of experimentation with animals, Kosdoba [12] and Ciantini [13] attributed to the thyroid gland and the adrenal glands a significant rôle in the regenerative processes. Wheeler and Adams [14] reported on a cholecystectomy incision wound which underwent retrogression at each menstrual cycle for two years and then healed shortly after bilateral ablation of the ovaries.

The clinical impression that cicatrization is retarded by the presence of remote collections of purulent material has received experimental support from the work of Carrel.[15] Turpentine was injected subcutaneously into dogs with surface wounds; coincident with the development of sterile abscesses healing diminished in rate or ceased, regaining its normal velocity on drainage. Subcutaneous administration of the sterile pus to other animals inhibited their reparative powers, thereby indicating that pus contains constituents inimical to healing.

It is on consideration of the many agents purported to influence the course of wound healing through local action that one enters a

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7. Lohr, W.: Med. Welt **8**:1273, 1934.

8. Roegholt, N.: Nederl. tijdschr. v. geneesk. **2**:3744, 1929.

9. Bird, C. E., and MacKay, E. M.: Surg., Gynec. & Obst. **54**:872, 1932.

10. Rabinowitch, I. M.: Simultaneous Respiratory Exchange and Blood Sugar Time Curves Obtained in Apparently Nondiabetic Patients with Nonhealing Wounds, Arch. Surg. **26**:696 (April) 1933.

11. Sullivan, E. A.: New England J. Med. **209**:241, 1933.

12. Kosdoba, A. S.: Arch. f. klin. Chir. **179**:435 and 551, 1934.

13. Ciantini, F.: Ann. ital. di chir. **12**:1119, 1933.

14. Wheeler, B. C., and Adams, D. S.: New England J. Med. **211**:630, 1934.

15. Carrel, A.: Compt. rend. Soc. de biol. **90**:333, 1924

moot field in surgical therapeutics. Beyond doubt a number of local factors are of significance. The degree and type of infection, the presence of foreign bodies, the trophic state of the tissues as regards blood and nerve supply, the amount of traumatism associated with dressing—all these indisputably affect the course of repair. But is there any valid basis for the claims concerning the therapeutic value of the horde of topical vulneraries, whether antiseptic or stimulant? Has the contention been substantiated that antiseptics further repair by exerting a selectively greater effect on bacteria than on the tissues? Do the supposed stimulants actually stimulate?

It would be impossible in a paper of this scope to evaluate critically or even to list the agents favorably advocated as stimulants of repair. Those based on Hammett's [16] work on the sulfhydryl radical include thiocresol, thioglycerol, cysteine, glutathione and insulin applied locally. Good results have been claimed for many physical agents: roentgen rays, ultraviolet rays, infra-red rays, diathermy, oxygen and carbon dioxide gas. Several investigators have employed embryonic extract and allantoic fluid, because of their admitted propensities for the stimulation of growth. Antigenic substances, such as bacterial filtrates and protein broths, as well as bacteriophages, have been used. A few hormones and vitamins have been applied locally, such as parathyroid extract, thyroid and testicular extracts, cod liver oil and viosterol. Still other advocated stimulants are peruvian balsam, irradiated petrolatum and amino-azotolueneazo-beta-naphthol, the active ingredient in scarlet red ointment. It has even been seriously proposed to treat wounds with the inner lining membrane of the hen's egg.

METHODS FOR EVALUATION OF STIMULANTS OF REPAIR

While certain of the purported stimulants of healing have been subjected to experimentation on animals, the evidence in behalf of the great number rests on clinical observation. The customary experimental procedure has been to prepare two bilaterally symmetrical wounds, one serving as a test object and the other as a control, and then to compare the length of the periods required for healing.

Before accepting conclusions drawn from results obtained by this technic one may well raise the following questions: 1. Will the time required for healing be precisely identical for two corresponding wounds similarly treated, and if not, what are the limits of expected variation? 2. How significant are the errors introduced by slight differences in size of the wounds and in other factors which are acting but presumably constant? 3. If the two preceding questions cannot be ruled out as

16. Hammett, F. S.: Protoplasma **7**:297, 1929.

inconsequential, what number of favorable observations is required to establish statistically the superiority of a particular substance under investigation?

A similar trend of thought is applicable to those studies in which results are derived from the examination of histologic sections. If one may require that inferences based on experiments with animals adequately meet the aforementioned criteria, it must be concluded that therapeutic efficacy has not been convincingly demonstrated for most of the proposed vulneraries tested by this method.

Likewise, the possibility of error has not been adequately eliminated in many reports advocating substances as stimulants of wound repair after apparently successful clinical trial. A fair number of the reports can be classified only as enthusiastic but uncontrolled impressions. For the most part, however, the conclusions drawn are founded on encouraging response of the wound to the application of a test agent, either in contrast to the effects of other materials used alternately or after a previous period of resistance to healing. It is difficult to estimate the magnitude of individual subjectivity in such observations. Furthermore, although there may occur a favorable response coincident with the institution of a particular mode of therapy, a causal relationship is not thereby established. Not only can a number of factors at a distance from a wound influence the course of its repair, as previously pointed out, but at the present time knowledge of these factors can hardly be regarded as complete. Consequently, the assumption that these forces remain constant throughout long intervals is at least doubtful, and an equal degree of doubt must extend to the conclusions dependent on such an assumption.

It is evident, then, that reliable assessment of the so-called wound stimulants requires more accurate methods of evaluation than those generally employed. The problem demands a quantitative approach. From studies of superficial, chemically sterilized wounds in man and in animals, Carrel [17] and his associates demonstrated wound repair to be an exponential function, with the rate at any given time governed by two intrinsic factors, the area of the wound and the age of the patient. The curves of normal wound healing presented by Carrel establish that the rate of healing is proportional to the area of the wound and decreases with the age of the patient. Du Noüy [18] expressed mathematically the interrelationships among these elements; his formula permits the prediction of the period in which a wound should normally heal and the calculation of the expected area of the wound at any time during the

17. Carrel, A., and Hartmann, A.: J. Exper. Med. **24**:429, 1916.

18. Du Noüy, P. L.: J. Exper. Med. **24**:461 (Nov.) 1916.

course of repair. In his article on acute empyema Heuer[19] stated: "Foulger has repeatedly predicted the date of healing of empyemic cavities from this formula and with a fair degree of accuracy." The work of Carrel and Du Noüy published in 1910 constitutes practically the only quantitative contribution to the problem of wound repair in man.

It is my belief that the existing controversy as to the place of topical agents in the treatment of wounds has resulted from the failure to apply quantitative considerations in the determination of their worth. Consequently, I adopted the following procedure in order to ascertain on the basis of precise measurement the clinical effects of a selected list of dressings.

My investigation was carried out on a series of sixteen patients, all in good general health unless otherwise indicated. The wounds studied differed in size and etiology, but each was of the type regarded as surgically clean. Each wound was dressed with two or more of the substances under investigation during alternate periods of varying duration. Under these conditions I have followed the course of healing, taking measurements of changes both in area and in volume at frequent intervals.

The area was obtained by placing a small celluloid film directly on the wound and tracing the line of union between the epithelial edge and the granulating surface. This tracing was then transferred to a sheet of paper, and the area was determined with a planimeter. Volume was determined by pouring a mold with sterilizable material which assumed the exact configuration of the granulating tissue and the surface of which could be trimmed to conform to the contour of the body. Cultures were taken from time to time to follow the bacteriologic status of the wound. From the data thus collected I plotted for each wound studied a curve representing the course of its healing under the successive local dressings.

The data were then evaluated on the following basis:

The broken line in chart 1 indicates the observed rate of healing of a wound when materials *A* and *B* were applied during alternate periods of the designated length. It is apparent that the curve of repair for this hypothetic wound is not geometric in form, but it is possible to draw a smooth curve showing the average rate of healing throughout the entire period of cicatrization. The solid line (chart 1) represents what I have arbitrarily considered to be the average rate of healing. For any single period it is possible to compare the slope of the broken line showing the actual rate of healing during that period with the

19. Heuer, in Graham, E. A.; Singer, J. J., and Ballon, H. C.: Surgical Diseases of the Chest, Philadelphia, Lea & Febiger, 1935.

curve indicating the average rate of healing. In this way I have classified healing during each period of observation as accelerated, average or retarded. Clearly this method evaluates the two substances applied only in terms of each other; it affords no comparison between the observed rate of healing and a theoretically normal rate. I may say, however, that any agent which is truly a stimulant will consistently increase the velocity of healing as compared with the average rate under the existing conditions. Furthermore, Carrel's [17] work on the velocity of normal repair has demonstrated that the slope of the curve at the onset of healing tends to be vertical, then becomes progressively less steep and ultimately approaches the horizontal. Therefore, the action

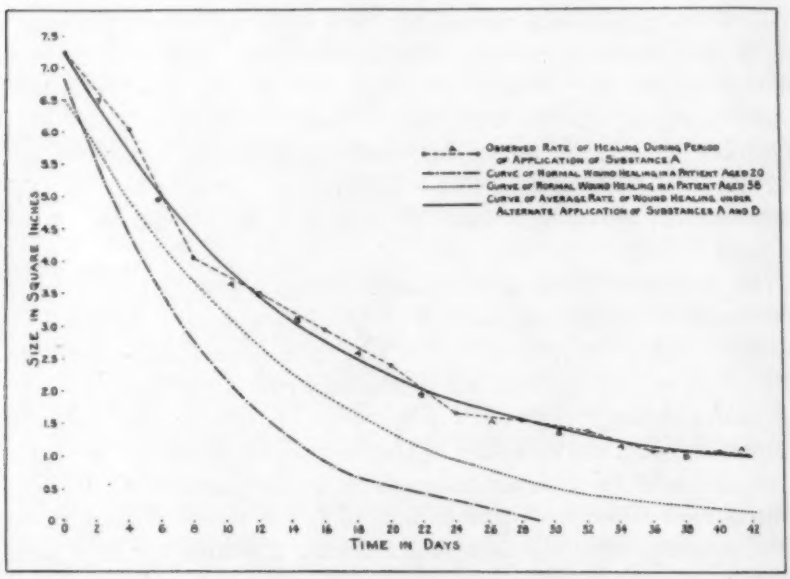
Observed Rate of Healing During Period of Application of Substance A
Curve of Normal Wound Healing in a Patient Aged 20
Curve of Normal Wound Healing in a Patient Aged 58
Curve of Average Rate of Wound Healing under Alternate Application of Substances A and D
Size in Square Inches
Time in Days

Chart 1.—Curves of wound healing.

of a stimulant should be most readily discernible in the later stages of wound healing, when one may expect the curve of repair to assume a horizontal direction.

The following practices were adopted in order to control to the greatest possible degree the influence of extraneous factors on the results obtained. In each patient studied an effort was made to maintain the diet and the intake of water at an approximately constant level, and the state of general health was carefully checked from time to time. So far as the time required for healing permitted, the agents tested on any particular wound were repeatedly applied, so that favorable and unfavorable influences exerted by nonlocal forces might mutually compensate. Two patients had multiple wounds, allowing comparison of

the effects obtained by simultaneous treatment with different modes of dressing. The majority of substances reported on were applied to the wounds of five or more patients, the final evaluations being based on the composite results.

The substances which have been studied by the technic outlined may be divided into three groups:

1. Admittedly inert agents: Petrolatum gauze, physiologic solution of sodium chloride and dry gauze dressing.

2. Antiseptic agents: 1:1,000 solution of merthiolate, 1:2,000 merthiolate ointment, 4 per cent solution of mercurochrome, zinc perox-

TABLE 1.—*Wound Resulting in G. H. from Removal for Biopsy of Acutely Inflamed Lymph Nodes (Right Inguinal Region)*

Date	Dressing	Period of Application, Days	Volume of Wound, Cc.			Rate of Healing
			Start	End	Change	
9/1 to 9/3	Dry packing and dressing...	2	9.6	9.6	0	Retarded
9/3 to 9/5	Dry packing and dressing...	2	9.6	9.1	0.5	Average
9/5 to 9/7	Dry packing and dressing...	2	9.1	7.5	1.6	Accelerated
9/1 to 9/7	Summary of period with dry dressing.....	6	9.6	7.5	2.1	
9/7 to 9/10	Wet merthiolate.....	3	7.5	6.7	0.8	Average
9/10 to 9/12	Wet merthiolate.....	2	6.7	6.6	0.1	Retarded
9/12 to 9/14	Wet merthiolate 24 hours....	2	6.6	6.1	0.5	Average
9/7 to 9/14	Summary of period with wet merthiolate.....	7	7.5	6.1	1.4	
9/14 to 9/17	Dry dressing.....	3	6.1	6.1	0	Retarded
9/17 to 9/19	Wet merthiolate.....	2	6.1	4.7	1.4	Accelerated
9/19 to 9/21	Dry dressing.....	2	4.7	4.9	—0.2	Retarded
9/21 to 9/24	Wet merthiolate.....	3	4.9	4.0	0.9	Accelerated
9/24 to 9/27	Dry dressing.....	3	4.0	2.6	1.4	Accelerated
9/27 to 10/1	Wet merthiolate.....	4	2.6	3.2	—0.6	Retarded
10/1 to 10/4	Dry dressing.....	3	3.2	2.4	0.8	Average
10/4 to 10/8	Wet merthiolate.....	4	2.4	1.7	0.7	Average
10/8 to 10/11	Wet sodium chloride.....	3	1.7	1.0	0.7	Average
10/11 to 10/15	Wet merthiolate.....	4	1.0	0.4*	0.6	Average

* Granulations filled in to maximal extent and wound almost epithelialized.

ide paste (consisting of zinc peroxide and water) and a paste consisting of zinc oxide, acacia and glycerin.

3. Presumably stimulating agents (some with antiseptic properties): 0.25 per cent thiocresol in solution and in ointment, irradiated petrolatum, a 0.6 per cent solution of allantoin, peruvian balsam and ultraviolet irradiation.

Among these substances major attention was devoted to merthiolate, mercurochrome, thiocresol, petrolatum gauze, solution of sodium chloride and dry gauze dressing.

OBSERVATION ON CASES

The following cases are typical of the entire series investigated:

CASE 1.—G. H., a man aged 32, had a wound resulting from excision for biopsy of a mass of inflamed lymph nodes in the right inguinal region. Through-

out the course of healing the wound showed healthy pink granulation tissue and was practically free from purulent discharge despite a positive culture of Staphylococcus aureus-haemolyticus and diphtheroid bacilli. During alternate periods of from two to seven days dressings of a 1 : 1,000 solution of merthiolate and dry gauze were applied, and the influence on the volume of the wound was measured.

The curve of healing (chart 2) reveals that neither dressing exerted a consistent effect on the velocity of repair. During the first six days, when dry gauze was used, the rate of healing as compared with the average rate was retarded for the first two days, average for the next two and accelerated for the last two. For the next seven days a solution of merthiolate was applied, and the rate of healing during that time was, in succession, average, retarded and average. During all the periods of observation in which dry dressing was employed, the rate of healing was average twice, accelerated twice and retarded three

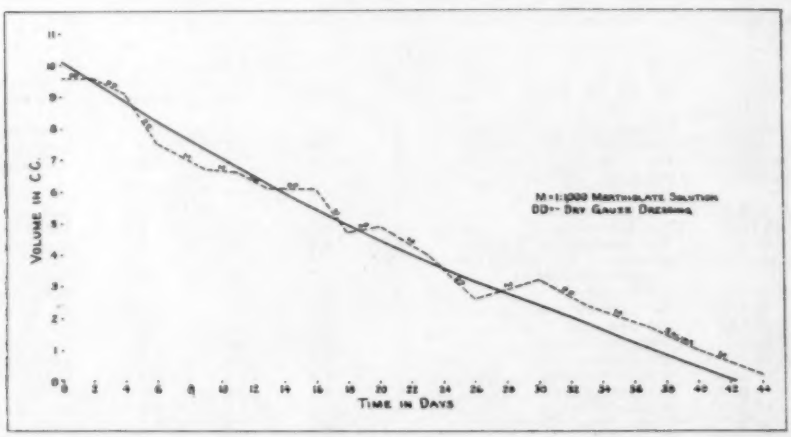

Chart 2 (case 1).—Curve of healing of biopsy wound of inguinal lymph nodes.

times. When merthiolate was employed, the rate of healing was average four times, accelerated twice and retarded twice.

Case 2.—W. J., a youth of 18 (table 2), as a result of plastic surgical procedures requiring multiple skin grafting, presented on one occasion shallow ulcers which had appeared simultaneously on the hand and the abdominal wall and a somewhat larger ulcer which had appeared at a later date on the hip. The former two ulcers were treated with merthiolate ointment, petrolatum gauze and dry dressing. To the latter ulcer only merthiolate ointment was applied. Progressive changes in the area of the wound were measured. The three ulcers presented vascular granulation tissue and were almost free from secretion.

Until the ulcer on the hand healed, it and the abdominal ulcer were similarly treated. The curve (chart 3) of repair for the ulcer on the hand was entirely geometric in form, notwithstanding treatment with merthiolate ointment, dry dressing and petrolatum gauze. During the corresponding period the curve for the identically dressed abdominal ulcer did not run parallel, but in the later stages of healing it became almost a straight line, despite alternate application of petrolatum gauze, merthiolate ointment and dry dressing. These observations suggest that factors other than the topical dressing governed the course of

TABLE 2.—*Effect of Dressings on Abdominal Ulcer Resulting from Removal of a Skin Graft, an Ulcer of the Hand Resulting from Partial Necrosis of a Skin Graft and an Ulcer of the Hip Resulting from Removal of a Skin Graft*

Date	Mode of Dressing	Period of Application, Days	Area of Abdominal Ulcer, Sq. In.			Area of Hand Ulcer, Sq. In.			Area of Hip Ulcer, Sq. In.		
			Start	End	Change	Start	End	Change	Start	End	Change
12/10 to 12/17	Merthiolate ointment	7	0.75	0.47	0.28	0.38	0.12	0.26			
12/17 to 12/24	Dry dressing	7	0.47	0.64	—0.17	0.12	0.12	0.00			
12/24 to 12/31	Merthiolate ointment	7	0.64	0.22	0.42	0.12	0.05	0.07			
12/31 to 1/7	Petrolatum gauze	7	0.22	0.25	—0.03	0.05	0.03	0.02			
1/7 to 1/14	Merthiolate ointment	7	0.25	0.26	—0.01	0.03	0.00	0.03			
1/14 to 1/21	Dry dressing	7	0.26	0.22	0.04	....	....	....			
1/21 to 1/28	Merthiolate ointment	7	0.22	0.11	0.11	....	....	....			
4/22 to 4/24	Merthiolate ointment	2	....	....	....	....	....	....	1.81	2.04	—0.23
4/24 to 4/27	Merthiolate ointment	3	....	....	....	....	....	....	2.04	1.74	0.30
4/27 to 4/30	Merthiolate ointment	3	....	....	....	....	....	....	1.74	1.58	0.16
4/30 to 5/3	Merthiolate ointment	3	....	....	....	....	....	....	1.58	1.50	0.08
5/3 to 5/6	Merthiolate ointment	3	....	....	....	....	....	....	1.50	1.21	0.29
5/6 to 5/10	Merthiolate ointment	4	....	....	....	....	....	....	1.21	1.22	—0.01
5/10 to 5/15	Merthiolate ointment	5	....	....	....	....	....	....	1.22	1.15	0.07
5/15 to 5/18	Merthiolate ointment	3	....	....	....	....	....	....	1.15	1.05	0.10
5/18 to 5/21	Merthiolate ointment	3	....	....	....	....	....	....	1.05	1.02	0.03
5/21 to 5/28	Merthiolate ointment	7	....	....	....	....	....	....	1.02	1.44	—0.42
5/28 to 5/31	Merthiolate ointment	3	....	....	....	....	....	....	1.44	0.48	0.96
5/31 to 6/4	Merthiolate ointment	4	....	....	....	....	....	....	0.48	0.87	—0.39
6/4 to 6/8	Merthiolate ointment	4	....	....	....	....	....	....	0.87	0.47	0.40
6/8 to 6/11	Merthiolate ointment	3	....	....	....	....	....	....	0.47	0.24	0.23
6/11 to 6/14	Merthiolate ointment	3	....	....	....	....	....	....	0.24	0.10	0.14
6/14 to 6/17	Merthiolate ointment	3	....	....	....	....	....	....	0.10	0.04	0.06
6/17 to 6/21	Merthiolate ointment	4	....	....	....	....	....	....	0.04	0.00	0.04

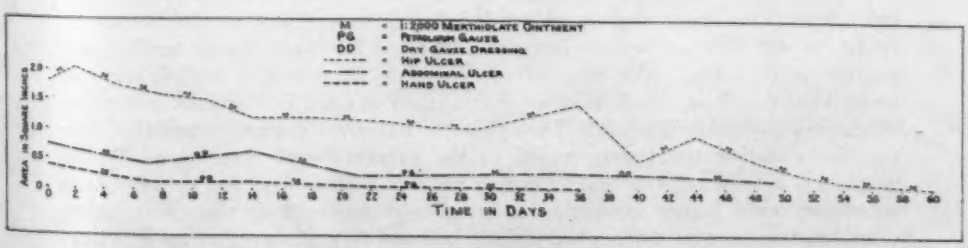

Chart 3 (case 2).—Curves of healing of ulcers on the hip, abdomen and hand, resulting from skin grafts.

repair and that the three agents employed exerted no significant effect. This point of view is further borne out by the curve of healing for the ulcer on the hip, which manifested a series of irregularities during constant treatment with merthiolate ointment.

Case 3.—C. J., an 11 year old boy (table 3), had traumatic ulcers on the left anterior tibia and the right ankle. Throughout the course of investigation the ulcer on the tibia on repeated culture showed hemolytic streptococci and Staph. aureus; a moderate purulent discharge persisted, although at all times the granulation tissue was richly vascular and healthy in appearance. During the period of study, the patient received a high calorie, vitamin-rich diet and gained in weight, and his general health underwent no evident changes. The substances used in local treatment comprised the antiseptic, merthiolate ointment, the inert

Table 3.—*Effect of Dressings on Ulcers over the Anterior Aspect of the Left Tibia and the Right Ankle Resulting from Trauma*

Date	Mode of Dressing	Period of Application, Days	Area of Ulcer, Sq. In.			Rate of Healing
			Start	End	Change	
	Left Anterior Tibial Ulcer					
4/29 to 5/ 1	Petrolatum gauze	2	2.38	2.34	0.04	Average
5/ 1 to 5/ 3	Petrolatum gauze	2	2.34	2.23	0.11	Average
5/ 3 to 5/ 7	Merthiolate ointment	4	2.23	2.63	—0.40	Retarded
5/ 7 to 5/10	Merthiolate ointment	3	2.63	2.30	0.33	Accelerated
5/10 to 5/13	Petrolatum gauze	3	2.30	2.74	—0.44	Retarded
5/13 to 5/16	Petrolatum gauze	3	2.74	3.46	—0.72	Retarded
5/16 to 5/21	Merthiolate ointment	5	3.46	4.23	—0.77	Retarded
5/21 to 5/23	Thiocresol ointment (0.25%)	2	4.23	3.68	0.55	Accelerated
5/23 to 5/26	Allantoin solution (0.6%)	3	3.68	1.40	2.28	Accelerated
5/26 to 5/28	Allantoin solution (0.6%)	2	1.40	1.43	—0.03	Retarded
5/28 to 5/31	Merthiolate ointment	3	1.43	1.42	0.01	Retarded
5/31 to 6/ 3	Merthiolate ointment	3	1.42	0.79	0.63	Accelerated
6/ 3 to 6/10	Merthiolate ointment	7	0.79	0.87	—0.08	Retarded
6/10 to 6/13	Merthiolate ointment	3	0.87	1.14	—0.27	Retarded*
6/13 to 6/17	Thiocresol ointment (0.25%)	4	1.14	0.95	0.19	Average
6/17 to 6/20	Dry dressing	3	0.95	0.90	0.05	Average
6/20 to 6/24	Allantoin solution	4	0.90	0.72	0.18	Average
6/24 to 6/27	Merthiolate ointment	3	0.72	0.20	0.52	Accelerated
	Ulcer on Right Ankle					
5/23 to 5/26	Thiocresol ointment (0.25%)	3	2.20	0.43	1.77	
5/26 to 5/28	Thiocresol ointment (0.25%)	2	0.43	0.08	0.35	
5/28 to 5/31	Thiocresol ointment (0.25%)	3	0.08	0.00	0.08	

* Ulcer accidentally bruised.

substances, petrolatum and dry gauze, and the stimulants, thiocresol ointment and allantoin solution. Measurement was made of the area of the wound.

Because of the irregular progress of healing in the tibial ulcer it is difficult to evaluate slight degrees of acceleration or retardation in the velocity of repair (chart 4); yet certain facts are definite. No single agent applied was constant in its action. The one marked "spike" in the course of healing occurred under local dressings, which at other times clearly exerted neither such deleterious effects nor favorable influence. The effects of thiocresol and of allantoin on both the ulcers during the twenty-second to the twenty-seventh day appeared most propitious, but the rates of healing during the next several days and on subsequent occasions hardly justify any enthusiastic claims regarding their therapeutic value. Considered as a whole, the observations indicate that whatever effect the local dressings may have produced on the velocity of repair, their action was inconstant and was probably overbalanced by other factors.

Case 4.—R. U., a woman of 31, subsequent to incision and drainage of abscesses in her thigh presented three wounds, placed anteriorly, medially and

laterally. There was originally a pure culture of hemolytic streptococci; for a time afterward these organisms and Staph. aureus predominated among a number of bacteria. The granulating surfaces tended to appear torpid and avascular throughout the period of observation. Secretion from the wound at first was

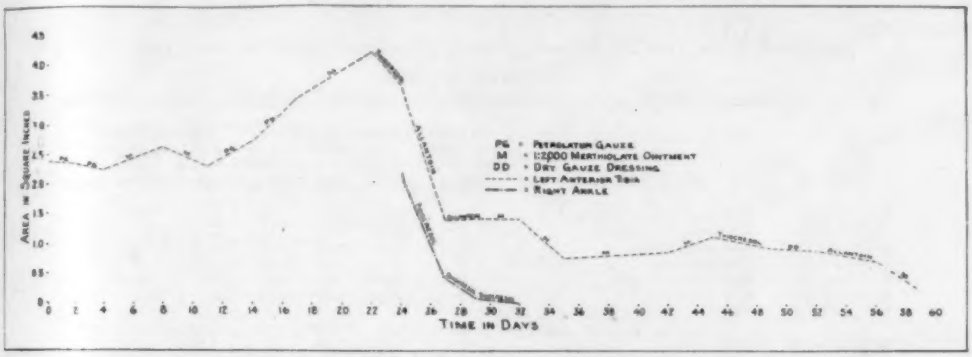

Chart 4 (case 3).—Curves of healing of ulcers of the left anterior tibia and the right ankle.

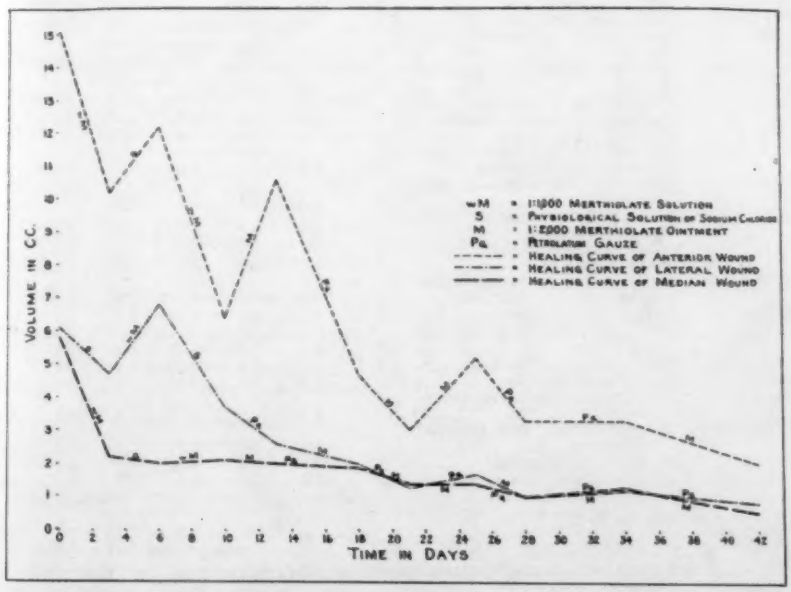
VOLUME IN CC.
TIME IN DAYS
wM = 1:1000 Merthiolate Solution
S = Physiological Solution of Sodium Chloride
M = 1:2000 Merthiolate Ointment
Pg = Petrolatum Gauze
Healing Curve of Anterior Wound
Healing Curve of Lateral Wound
Healing Curve of Median Wound

Chart 5 (case 4).—Curves of healing of incision wounds in cellulitis of the thigh.

moderate; later it diminished in quantity. To each wound, merthiolate and either physiologic solution of sodium chloride or petrolatum gauze were applied alternately. During any single period the anterior and the medial wound were dressed similarly, while the alternate dressing was used on the lateral wound.

If each curve (chart 5) is looked at separately considerable irregularity can be noted in the rate of repair, but no consistent relationship can be observed

between the dressing used and the slope assumed by the curve. When the three curves are viewed together, a trend toward parallelism can be detected. This correspondence differs in degree and is not invariable, but it is definitely present. Consideration of the individual curves suggests that healing occurred by fits and starts. The occurrence of these fits and starts simultaneously in the three

TABLE 4.—*Effect of Dressings on a Decubitus Ulcer in the Right Trochanteric Area*

Date	Mode of Dressing	Period of Application, Days	Volume of Wound, Cc.			Area of Wound, Sq. In.		
			Start	End	Change	Start	End	Change
8/11 to 8/17	Wet merthiolate	2	30.0	24.0	6.0	6.4	6.3	0.1
8/13 to 8/15	Dry gauze dressing	2	24.0	22.9	1.1	6.3	6.5	−0.2
8/15 to 8/17	Wet merthiolate	2	22.9	24.0	−1.1	6.5	7.5	−1.0
9/ 8 to 9/17	Dry dressing	9	9.5	9.0	0.5	4.9	4.6	0.3
9/17 to 9/19	Wet merthiolate	2	9.0	9.5	−0.5	4.6	4.7	−0.1
9/19 to 9/21	Dry dressing	2	9.5	8.9	0.6	4.7	4.1	0.6
9/21 to 9/24	Thiocresol 48 hours; solution of sodium chloride 24 hours.	3	8.9	6.3	2.6	4.1	3.9	0.2
9/24 to 9/26	Thiocresol	2	6.3	11.0	−4.7	3.9	3.6	0.3
9/21 to 9/26	Thiocresol (summary)	5	8.9	11.0	−2.1	4.1	3.6	0.5
9/26 to 10/1	Solution of sodium chloride	5	11.0	10.2	0.8	3.6	3.2	0.4
10/1 to 10/3	Thiocresol	2	10.2	8.0	2.2	3.2	3.0	0.2
10/3 to 10/9	Solution of sodium chloride	6	8.0	3.0	5.0	3.0	3.9	−0.9*
10/9 to 10/13	Merthiolate solution and ointment	4	3.0	2.9	0.1	3.9	4.3	−0.4
10/13 to 10/17	Petrolatum gauze	4	2.9	9.8	−6.9	4.3	3.7	0.6
10/17 to 10/20	Merthiolate ointment	3	9.8	7.9	1.9	3.7	3.4	0.3
10/20 to 10/24	Merthiolate ointment	4	7.9	5.4	2.5	3.4	2.8	0.6
10/17 to 10/24	Merthiolate ointment (summary)	7	9.8	5.4	4.4	3.7	2.8	0.9
10/24 to 10/31	Mercurochrome and petrolatum	7	5.4	6.2	−0.8	2.8	2.6	0.2
11/ 1 to 11/ 8	Ultraviolet irradiation and petrolatum gauze dressing	7	6.2	6.6	−0.4	2.6	2.8	−0.2
11/ 8 to 11/12	Merthiolate ointment	4	6.6	7.4	−0.8	2.8	...	...
11/13 to 11/19	Ultraviolet irradiation and merthiolate ointment	6	7.4	7.1	0.3	...	3.0	...
11/19 to 11/23	Ultraviolet irradiation and petrolatum gauze	4	7.1	5.3	1.8	3.0	3.3	−0.3
11/23 to 11/28	Ultraviolet irradiation and dry dressing	5	5.3	5.7	−0.0	3.3	3.9	−0.6
11/28 to 12/ 6	Merthiolate ointment	8	5.7	2.7	3.0	3.9	2.6	1.3
12/ 6 to 12/13	Petrolatum gauze	7	2.7	3.6	−0.9	2.6	3.8	−1.2
12/13 to 12/26	Irradiated petrolatum ointment	13	3.6	4.7	−1.1	3.8	3.9	−0.1
12/26 to 1/ 3	Merthiolate ointment	8	4.7	4.9	−0.2	3.9	4.4	−0.5
1/ 3 to 1/10	Mercurochrome and petrolatum gauze	7	4.9	1.95	+2.95	4.4	4.4	0
1/10 to 1/18	Merthiolate ointment	8	1.95	2.4	−0.45	4.4	3.8	0.6
1/18 to 1/25	Merthiolate ointment	7	2.4	1.8	0.6	3.8	3.6	0.2
1/10 to 1/25	Merthiolate ointment (summary)	15	1.95	1.8	0.15	4.4	3.6	0.8
1/25 to 2/ 1	Mercurochrome and petrolatum gauze	6	1.8	3.55	−1.75	3.6	3.8	−0.2
2/ 1 to 2/ 9	Merthiolate ointment	8	3.55	2.7	0.85	3.8	4.0	−0.2
2/ 9 to 2/15	Peruvian balsam	6	2.7	3.3	−0.6	4.0	3.2	0.8

* Laminectomy on 10/5.

wounds at frequent intervals, notwithstanding the differences in the mode of dressing, forces the conclusion that the rhythm of healing was set mainly by factors acting at a distance rather than locally. As the parallelism among the curves is not constant, there were times when local forces must have predominated, but there is little evidence that the type of dressing materially affected these forces. These observations apply to the curves of healing based on measurement of both the volume of the wound, as shown in chart 5, and the area of the wound.

CASE 5.—J. F., a boy of 14 with a tumor of the spinal cord extending from the upper thoracic segments to the cauda equina, acquired three large decubitus ulcers, located over each hip and the sacrum. Throughout the period of investi-

TABLE 5.—*Effect of Dressings on a Decubitus Ulcer in the Left Trochanteric Area*

Date	Mode of Dressing	Period of Application, Days	Volume of Ulcer, Cc.			Area of Ulcer, Sq. In.		
			Start	End	Change	Start	End	Change
8/13 to 8/15	Dry dressing	2	10.0	10.3	—0.3	1.5	1.5	0.0
8/15 to 8/17	Wet merthiolate	2	10.3	12.0	—1.7	1.5	1.4	0.1
9/ 8 to 9/10	Dry dressing	2	2.5	3.1	—0.6	1.3	1.5	—0.3
9/10 to 9/13	Dry dressing	3	3.1	2.8	0.3	1.5	1.4	0.1
9/13 to 9/17	Dry dressing	4	2.8	4.8	—2.0	1.4	1.3	0.1
9/ 8 to 9/17	Dry dressing (summary)	9	2.5	4.8	—2.3	1.2	1.3	—0.1
9/17 to 9/19	Wet merthiolate	2	4.8	2.1	2.7	1.3	1.2	0.1
9/19 to 9/21	Dry dressing	2	2.1	3.3	—1.2	1.2	1.4	—0.2
9/21 to 9/24	Thiocresol 2 days, solution of sodium chloride 1 day	3	3.3	4.6	—1.3	1.4	1.3	0.1
9/24 to 9/26	Thiocresol	2	4.6	3.3	1.3	1.3	1.1	0.2
9/21 to 9/26	Thiocresol	5	3.3	3.3	0.0	1.4	1.1	0.3
9/26 to 10/1	Solution of sodium chloride	5	3.3	2.3	1.0	1.1	1.0	0.1
10/ 1 to 10/3	Thiocresol	2	2.3	1.7	0.6	1.0	1.0	0.0
10/ 3 to 10/6	Solution of sodium chloride	3	1.7	3.7	—2.0	1.0	1.2	—0.2*
10/ 6 to 10/9	Solution of sodium chloride	3	3.7	2.6	1.1	1.2	1.5	—0.3
10/ 3 to 10/9	Solution of sodium chloride (summary)	6	1.7	2.6	—0.9	1.0	1.5	—0.5
10/ 9 to 10/13	Merthiolate ointment	4	2.6	5.5	—2.9	1.5	1.2	0.3
10/13 to 10/17	Petrolatum gauze	4	5.5	5.6	—0.1	1.2	1.4	—0.2
10/17 to 10/20	Merthiolate ointment	3	5.6	3.6	2.0	1.4	1.8	—0.4
10/20 to 10/24	Merthiolate ointment	4	3.6	2.4	1.2	1.8	1.5	0.3
10/17 to 10/24	Merthiolate ointment (summary)	7	5.6	2.4	3.2	1.4	1.5	—0.1
10/24 to 10/31	Mercurochrome and petrolatum gauze	7	2.4	3.1	—0.7	1.5	1.4	0.1
11/ 1 to 11/ 8	Ultraviolet irradiation and petrolatum gauze	7	3.1	5.3	—2.2	1.4	1.7	—0.3
11/ 8 to 11/12	Merthiolate ointment	4	5.3	3.8	1.5	1.7	...	...
11/12 to 11/19	Ultraviolet irradiation and merthiolate ointment	7	3.8	2.8	1.0	...	1.9	...
11/19 to 11/23	Ultraviolet irradiation and petrolatum gauze	4	2.8	2.4	0.4	1.9	1.6	0.3
11/23 to 11/28	Ultraviolet irradiation and dry dressing	5	2.4	3.4	—1.0	1.6	1.6	0.0
11/28 to 12/ 6	Merthiolate ointment	8	3.4	0.8	2.6	1.6	1.5	0.1
12/ 6 to 12/13	Petrolatum gauze	7	0.8	1.4	—0.6	1.5	2.4	—0.9
12/13 to 12/26	Irradiated petrolatum ointment	13	1.4	2.1	—0.7	2.4	1.9	0.5
12/26 to 1/ 3	Merthiolate ointment	8	2.1	1.3	0.8	1.9	2.1	—0.2
1/ 3 to 1/10	Mercurochrome and petrolatum gauze	7	1.3	1.2	0.1	2.1	1.7	0.4
1/10 to 1/18	Merthiolate ointment	8	1.2	1.0	0.2	1.7	2.0	—0.3
1/18 to 1/25	Merthiolate ointment	7	1.0	1.3	—0.3	2.0	2.1	—0.1
1/10 to 1/25	Merthiolate ointment (summary)	15	1.2	1.3	—0.1	1.7	2.1	—0.4
1/25 to 2/ 1	Mercurochrome and petrolatum gauze	7	1.3	1.3	0.0	1.7	2.1	—0.1
2/ 1 to 2/ 9	Merthiolate ointment	8	1.3	1.3	0.0	2.2	2.5	—0.3
2/ 9 to 2/15	Peruvian balsam	6	1.3	3.1	—1.8	2.5	2.9	—0.4

* Laminectomy on 10/5.

gation, of approximately six months, there was an irregular fever, the temperature ranging from 97 to 101 F., probably due to pyelonephritis, but the patient remained in a good nutritional state. Laminectomy was performed twice, revealing almost total destruction of the cord, and no functional recovery followed incomplete removal of the tumor. Studies on the rate of healing of the three ulcers were not instituted until all were clean and granulating. The observations are summarized in tables 4, 5 and 6.

Similar reparative phenomena occurred in the three wounds. After initial rapid cicatrization the velocity of healing became exceedingly slow. Ultimately the sacral ulcer became entirely epithelialized, but when the two trochanteric ulcers had decreased to a certain size, the process of repair could not be brought to completion. Extreme care was employed to minimize the effects of pressure: the patient rested constantly on either an air ring or an air mattress; the ulcers were further protected with soft cotton pads, and the position was changed every two hours, day and night. Notwithstanding these measures and persistent treatment with local agents—antiseptic, stimulant and inert—it was impossible to effect total healing during five months of effort, after which the patient was transferred from the hospital. The ulcers showed fluctuation in size from time to time, but the tables indicate that to none of the substances tested can a consistent therapeutic effect be attributed. Several surgical consultants commented on the favorable appearance of the ulcers; almost invariably the granulations were clean and red, and

TABLE 6.—*Effect of Dressings on a Decubitus Ulcer over the Left Sacrum*

Date	Mode of Dressing	Period of Application, Days	Volume of Ulcer, Cc.			Area of Ulcer, Sq. In.		
			Start	End	Change	Start	End	Change
8/ 8 to 8/10	Dry dressing	2	10.3	9.8	0.5	3.3	3.5	—0.2
8/10 to 8/11	Dry dressing	1	9.8	9.7	0.1	3.5	3.3	0.2
8/ 8 to 8/11	Summary of dry dressing	3	10.3	9.7	0.4	3.3	3.3	0.0
8/11 to 8/13	Wet merthiolate	2	9.7	11.8	—2.1	3.3	3.2	0.1
8/13 to 9/15	Dry dressing	2	11.8	8.9	2.9	3.2	3.1	0.1
8/15 to 8/17	Wet merthiolate	2	8.9	10.0	—1.1	3.1	3.6	—0.5*
9/ 8 to 9/10	Dry dressing	2	...	...	...	1.3	1.3	0.0
9/10 to 9/13	Dry dressing	3	...	...	...	1.3	1.2	0.1
9/13 to 9/17	Dry dressing	4	...	...	...	1.2	1.3	—0.1
9/ 8 to 9/17	Summary of dry dressing	9	...	...	...	1.3	1.3	0.0
9/17 to 9/19	Wet merthiolate	2	...	...	...	1.3	1.3	0.0
9/19 to 9/21	Dry dressing	2	...	...	...	1.3	1.0	0.3
9/21 to 9/24	Thiocresol 48 hours; solution of sodium chloride 24 hours	3	...	...	...	1.0	0.9	0.1
9/24 to 9/26	Thiocresol	2	...	...	...	0.9	1.1	—0.2
9/21 to 9/26	Summary of thiocresol period	5	...	...	...	1.0	1.1	—0.1
9/26 to 10/ 1	Wet sodium chloride	5	...	...	...	1.1	1.3	—0.2
10/ 1 to 10/ 3	Thiocresol	2	...	...	...	1.3	1.1	0.2
10/ 3 to 10/ 6	Solution of sodium chloride	3	...	...	...	1.1	0.8	0.3†
10/ 6 to 10/ 9	Petrolatum gauze	3	...	...	...	0.8	0.9	—0.1
10/ 9 to 10/13	Merthiolate ointment	4	...	...	...	0.9	0.5	0.4
10/13 to 10/17	Petrolatum gauze	4	...	...	...	0.5	0.05	0.45

* Laminectomy.
† Laminectomy on 10/5.

a fresh epithelial margin was present. It must be concluded that under the existing trophic conditions, the agents employed locally had insufficient effect on the processes of repair to bring about healing.

SUMMARY OF OBSERVATIONS ON WOUNDS

Tables 7 and 8 present a summary of the data obtained with all the agents investigated on the entire series of patients. In the instances in which the wound studied failed to heal (not including those in which observations were discontinued during the progress of satisfactory repair) the plotting of curves of healing was obviously impossible, which necessitated a different method of evaluation. Instead of classifying repair as accelerated, retarded or average for a given period of observation, I have assessed the agent applied locally on the basis of whether

the size of the wound increased, decreased or underwent no change. With both types of wounds, however, healing and nonhealing, the results were essentially identical. The observation made on the individual

TABLE 7.—*Effect of Dressings on Wounds Which Underwent Healing*

Dressing	Number of Patients Treated	Observed Effect on Wounds: Number of Observations	Observed Effect on Wounds: Rate of Healing: Accelerated	Retarded	Average	Percentage Effect on Rate of Healing: Accelerated	Retarded	Average
Merthiolate ointment 1:2,000	9	68	27	23	18	39.7	33.8	26.5
Merthiolate solution 1:1,000	5	26	10	8	8	38.4	30.8	30.8
Petrolatum gauze	6	36	13	11	12	36.1	30.6	33.3
Dry dressing	7	19	4	9	6	21.1	47.4	31.5
Physiologic solution of sodium chloride	2	11	4	3	4	36.4	27.3	36.4
Mercurochrome and petrolatum gauze	3	8	..	3	5	....	37.5	62.5
Thiocresol ointment (0.25%)	3	10	1	5	4	10.0	50.0	40.0
Zinc peroxide paste	4	6	..	4	2	....	66.7	33.3
Irradiated petrolatum ointment	1	2	..	1	1	....	50.0	50.0
Peruvian balsam	1	2	1	1	..	50.0	50.0	....
Zinc oxide paste boot	1	1	..	..	1	....	....	100.0
Allantoin solution (0.6%)	2	4	2	1	1	50.0	25.0	25.0
		193	62	69	62	32.1	35.7	32.1

TABLE 8.—*Effect of Dressings on Wounds Which Failed to Heal*

Dressing	Number of Patients Treated	Observed Effect on Wounds: Number of Observation Periods	Observed Effect on Wounds: Size of Wound: Decreased	Increased	Unchanged	Percentage Effect on Wound Size: Decreased	Increased	Unchanged
Merthiolate ointment 1:2,000	3	51	31	19	1	60.8	37.3	1.9
Merthiolate solution 1:1,000	1	15	6	8	1	40.0	53.3	6.7
Petrolatum gauze	3	15	4	11	..	26.7	73.3	...
Dry dressing	2	27	16	9	2	59.3	33.3	7.4
Physiologic solution of sodium chloride	1	12	7	5	..	58.3	41.7	...
Mercurochrome and petrolatum gauze	2	15	6	7	2	40.0	46.7	13.3
Thiocresol solution	1	15	11	3	1	73.3	20.0	6.7
Zinc peroxide ointment	1	1	1	..	..	100.0	....	...
Irradiated petrolatum ointment	2	7	2	5	..	28.6	71.4	...
Peruvian balsam	1	4	1	3	..	25.0	75.0	...
Zinc oxide paste boot	1	1	1	..	..	100.0	....	...
Ultraviolet irradiation	1	4	..	3	1	....	75.0	25.0
Ultraviolet irradiation and petrolatum gauze	1	8	3	5	..	37.5	62.5	...
Ultraviolet irradiation and merthiolate ointment	1	2	2	..	..	100.0	....	...
		177	91	78	8	51.4	44.1	4.5

patient that the local dressing did not consistently affect the course of cicatrization is substantiated by the sum total of results with each agent at all extensively tested.

In wounds which healed comparison may be made between the effect of merthiolate ointment and that of petrolatum gauze, which was used as a control, and between the effect of a solution of merthiolate and

that of physiologic solution of sodium chloride, which was used as a control. In thirty-six observations on six patients, repair under a dressing of petrolatum gauze was accelerated in 36.1 per cent, retarded in 30.6 per cent and of average rate in 33.3 per cent. The effect of merthiolate ointment appears slightly superior, healing being accelerated in 39.7 per cent, retarded in 33.8 per cent and average in 26.5 per cent of sixty-eight applications on nine patients. Similarly, when the effect of a physiologic solution of sodium chloride was contrasted with that of a solution of merthiolate a slight superiority was noted in favor of the latter. Yet a decided effect on healing can hardly be attributed to any of these four agents, since there was approximate correspondence in the percentage incidence of an accelerated, average or retarded rate of repair.

With dry gauze dressing, mercurochrome and thiocresol ointment healing was preponderantly either retarded or of average velocity; hence these substances appear to exert a somewhat detrimental action. In a number of wounds which had been cicatrizing steadily during several successive periods of observation, it was noted that the application of mercurochrome coincided with definite retardation in the rate of healing. Thiocresol contains the sulfhydryl group, which Hammett and Reimann considered the specific hormone for cellular proliferation. Not only these authors but Brunsting and Simonsen,[20] Birnbaum[21] and Sutton[22] have reported favorably on the value of sulfhydryl preparations. In my experience, however, I have found during ten periods of observation on three patients treated with thiocresol dressings that healing was accelerated only once, retarded five times and average four times.

The study of wounds which progressed to healing comprised treatment with twelve different local dressings during a total of one hundred and ninety-three periods of observation. The agents used either were admittedly inert or were presumed to further the reparative functions through a stimulant or antiseptic action. No single substance proved of outstanding worth or particularly detrimental to repair. The effect of the entire group was to accelerate the velocity of healing in 32.1 per cent, to retard it in 35.7 per cent and not to alter it in 32.1 per cent of the instances in which these vulneraries were employed. Therefore, it must be concluded that whatever slight effect these substances may exert, they do not significantly influence the course of healing.

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20. Brunsting, L. A., and Simonsen, D. G.: Cutaneous Ulcers Treated by Sulphydryl Containing Amino-Acid Cysteine, J. A. M. A. **101**:1937 (Dec. 16) 1933.

21. Birnbaum, I. R.: Ann. Surg. **96**:467, 1932.

22. Sutton, L. E.: Thioglycerol: A More Stable Sulphydryl Compound for Use in the Healing of Wounds, J. A. M. A. **104**:2168 (June 15) 1931.

On consideration of the results obtained in the investigation of nonhealing wounds, a similar conclusion is reached. Not every agent, however, had an identical effect on the two types of wounds—healing and nonhealing. While with the former class of wounds, both merthiolate ointment and merthiolate solution were somewhat superior to their respective controls, petrolatum gauze and physiologic solution of sodium chloride, with the latter type their actions appear divergent, the ointment having a favorable influence on healing and the solution an unfavorable influence as compared with the controls. Furthermore, in contrast to the findings regarding wounds which healed, dry gauze dressing seems superior to petrolatum gauze, and thiocresol apparently is a definite stimulant.

It will be observed, however, on more detailed scrutiny of these results that the two substances most thoroughly tested were merthiolate ointment and dry gauze dressing. The effects of these agents on the rate of healing are substantially alike; neither produced a marked acceleration in the velocity of repair. Throughout this study I have noted that as the number of periods of observation in the evaluation of any given material increased, there occurred a counterbalancing of favorable and unfavorable results until the two approximated. Examination of the agents listed in the tables and their respective number of periods of observation reveals this tendency. The necessity for accumulating a great body of observations before drawing conclusions as to the value of any preparation and the likelihood of fallacious conclusions after only a limited number of observations are thus strongly indicated. These considerations probably account for the difference in results obtained in the evaluation of the effects of certain agents on both healing and nonhealing wounds.

During the entire investigation on wounds which could not be caused to cicatrize totally, fourteen agents—antiseptic, stimulant and inert—were applied in one hundred and seventy-seven periods of observation; their effect was a decrease in the size of the wound in 51.4 per cent of the cases, an increase in 44.1 per cent and no change in 4.5 per cent. The values obtained with the antiseptic merthiolate ointment and the inert dry gauze dressing somewhat surpass the general average but reveal no markedly efficacious action on repair. Consequently, the statement seems warranted that in nonhealing wounds, just as in healing wounds, the agents tested by local application have not significantly affected the reparative functions.

Furthermore, I have found in the course of my work that no antiseptic ever sterilized or even significantly altered the cultural characteristics of any of the wounds studied, which were of the type surgically

clean but bacteriologically contaminated. Hill [23] reported the failure of a single application of a 2 per cent solution of mercurochrome to sterilize an infected wound. Both Carrel [24] and Wright [25] have expressed the conviction that antiseptics do not sterilize heavily infected wounds. Since infection admittedly inhibits repair, this failure of antiseptics to affect the cultural status of wounds affords confirmation on bacteriologic grounds for the point of view that I have reached on the basis of measurement, that these agents do not greatly influence the rate of healing.

My observations on the effect of local dressings on wound healing may be summarized as follows:

1. During the cicatrization of a given wound agents repeatedly applied locally during alternate periods have failed to influence the rate of repair in a consistent manner.

2. Among the substances studied in this investigation no single agent, irrespective of its nature, proved outstandingly favorable or unfavorable in its action.

3. A wound will heal or fail to heal regardless of the material applied locally. The effects exerted on the processes of repair by agents applied locally are of relatively minor significance and are outweighed by other forces, many of which are probably nonlocal.

EFFECT OF MERTHIOLATE ON TISSUES IN VITRO

In carrying out this investigation on local therapeutic agents I devoted particular attention to the recently introduced antiseptic merthiolate. Chemically this substance is the sodium salt of ethylmercurithiosalicylic acid. Tests of its antiseptic potency and toxicity have established that dilutions nontoxic to animals are bactericidally effective against cultures in vitro in the presence of serum. I have already presented the results of its clinical trial, in which a slight superiority over control agents, petrolatum gauze or physiologic solution of sodium chloride, was possibly manifested, but without demonstration that it caused any marked alteration in the course of healing.

In order to check this clinical evaluation, the degree of selectivity of the action of merthiolate on bacteria and on living cells was ascertained by studies in vitro.[26] The concept that the comparative toxicity to bacteria and to cells of the body provided the proper criterion for

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23. Hill, J. H.: The Action of Mercurochrome and Other Drugs on Normal Human Skin and in Infected Wounds, J. A. M. A. **105**:100 (July 13) 1935.

24. Carrel, A., and Dehelly, G.: Treatment of Infected Wounds, New York, Paul B. Hoeber, Inc., 1916.

25. Wright, A.: Brit. M. J. **2**:629, 1915.

26. The experiments on tissue cultures were performed in the laboratory of Dr. J. M. Hogue.

the assessment of an antiseptic was first practically applied by Lambert [27] in 1916 through the use of tissue cultures. Since that date cultures in vitro have been employed in determining the efficiency of antiseptics by Lambert and Meyer,[28] German,[29] Buchsbaum and Bloom [30] and Salle and Lazarus,[31] although no standard technic was followed. All these investigators, however, agreed in the finding that every antiseptic tested had a more deleterious effect on tissues than on bacteria.[32] Buchsbaum and Bloom [30] studied merthiolate and expressed their results in terms of an index of relative toxicity equal to the ratio of the greatest dilution that killed the bacterium used to the greatest concentration in which cells showed approximately normal growth. It was found that the index for merthiolate was 0.9, the highest obtained in a group including phenol, iodine, mercurochrome and metaphen, thereby establishing merthiolate as the least toxic of the agents evaluated, but not a theoretically ideal antiseptic (the ratio for which should exceed 1).

Since my work in this field will be reported in detail subsequently, I shall merely cite in brief the data pertaining to merthiolate. Using explants of skin from a chick embryo cultivated in a liquid medium, I determined: (1) the least concentration which killed Staph. aureus in the culture medium alone, (2) the least concentration which killed this organism in the presence of the explant and (3) the least concentration which was deleterious to the growth of the explant.

Under the experimental conditions established, dilutions of merthiolate up to 1:100,000 were invariably bactericidal in the culture medium alone. Yet in the presence of the explant a concentration of 1:20,000 was required to destroy the organism; with a concentration of 1:100,000 growth always occurred, and for intermediate ranges results depended on the size of the explant used in making the culture. Concerning the effect of merthiolate on the tissue alone, it was observed that dilutions up to 1:600,000 invariably killed the explant while dilutions of 1:1,200,000 still prevented normal growth, as indicated by control cultures.

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27. Lambert, R. A.: J. Exper. Med. **24**:683, 1916.

28. Lambert, R. A., and Meyer, J. R.: Proc. Soc. Exper. Biol. & Med. **23**:429, 1926.

29. German, W. J.: Effect of Some Antiseptics on Tissues in Vitro, Arch. Surg. **18**:1920 (April, pt. 2) 1929.

30. Buchsbaum, R., and Bloom, W.: Proc. Soc. Exper. Biol. & Med. **28**:1060, 1931.

31. Salle, A. J., and Lazarus, A. S.: Proc. Soc. Exper. Biol. & Med. **32**:665, 937, 1057, 1119 and 1481, 1935.

32. Salle and Lazarus have recently reported iodine in the form of compound solution of iodine to be more toxic in vitro to bacteria than to tissues.

These observations establish that there is a more toxic action by merthiolate on connective tissue and epithelial cells than on bacteria, but most striking is the marked depression in antiseptic potency produced by the concomitant presence of tissue and micro-organisms. In view of the great difference in conditions prevailing in wounds on the body and in cultures in vitro, it is my belief that these observations are not directly applicable to the problem of the influence of antiseptics on wound repair. None the less, this evidence must be regarded as indicating that such influence in all probability will not be favorable, a point of view consistent with the conclusions previously derived from the actual study of wound healing.

CONCLUSION

Through a method of quantitative evaluation of the effect of local agents on the velocity of wound repair it has been demonstrated that the substances tested, including antiseptics, stimulants and inert materials, failed to affect significantly the processes of repair. Factors other than the local dressing appear to play the dominant rôle in determining the rate of wound healing.

ESTRUS CYCLES IN MICE OF CANCEROUS AND NONCANCEROUS STRAINS

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It has been shown by Lacassagne [1] and more recently by Burrows [2] that carcinoma of the breast may be produced in male mice by the administration of large doses of estrogenic hormone. These observations are of great importance because this is the first instance of direct association of malignant neoplasia with an excess of a hormone normally produced by the organism. The question immediately arising is: Does spontaneous carcinoma of the breast in mice result from hypersecretion of estrogenic hormone over a long period?

As a result of the classic works of Allen,[3] and of Allen and Doisy and their associates,[4] the secretion of estrogenic hormone may be studied readily in the intact mouse by observation of the estrus cycle. Proestrus and estrus correspond to the period of ripening and the period of maximum activity of the graafian follicle. Metestrus and diestrus are periods in which no appreciable amount of estrogenic hormone is liberated.

Few reports are found in the literature of studies in which comparisons were made of estrus cycles in mice belonging to strains with high and low incidence of carcinoma of the breast. Lacassagne [5] mentioned briefly that in two strains—one in which carcinoma developed between the fourth and the sixth month of life and one in which it appeared between the tenth and the twelfth month—the average duration of estrus cycles varied considerably. In the former the cycle was regular and of the five day type; in the latter it was irregular and the periods of

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1. Lacassagne, A.: Apparition de cancers de la mamelle chez la souris mâle soumise à des injections de folliculine, Compt. rend. Acad. d. sc. **195**:630, 1932.
2. Burrows, Harold: Pathological Changes Induced in the Mamma by Estrogenic Compounds (Hunterian Lecture), Brit. J. Surg. **23**:191 (July) 1935.
3. Allen, E.: The Oestrous Cycle in the Mouse, Am. J. Anat. **30**:297, 1922.
4. Allen, E.; Doisy, E. A., and others: The Hormone of the Ovarian Follicle, Am. J. Anat. **34**:133, 1924.
5. Lacassagne, A., and Nyka, W.: A propos d'une pathogénie de l'adénocarcinome mammaire: recherches de la folliculine dans le colostrum, Compt. rend. soc. de biol. **116**:844, 1934.

heat were relatively brief. Harde [6] mentioned briefly that in strains in which the incidence of carcinoma was high the cycles were a little more prolonged than in the strains in which it was low. To be of real significance, however, marked consistent differences should be noted in the estrus cycles of different strains, for, as has been repeatedly shown, there is naturally a species variation and even an individual variation in length and type of the estrus cycle in mice.

The following observations were undertaken to compare the estrus cycles (follicular secretion) in three groups of mice, one composed of animals from a strain in which spontaneous carcinoma of the breast has never been observed, the second including mice belonging to a strain in which the incidence was high but which did not at the time of the experiment exhibit tumors of the breast and the third including animals of the same strain as those in group two which exhibited carcinoma of the breast during the period of observation.

EXPERIMENTATION

Material and Methods.—The mice used for study of the effects of various doses of theelin were albinos of unrecorded ancestry, obtained from a dealer.

The mice of the strain in which the incidence of cancer was high were obtained through the kindness of Dr. C. C. Little from the Roscoe B. Hyde Memorial Laboratory, in Bar Harbor, Maine. They were of the dilute brown strain, in which the incidence of cancer is stated to be 58.68 per cent. This strain (Little dba) has been fully described.[7] The mice of noncancerous strain, also obtained from Dr. Little, were black mice of the strain C 57. No tumors have been observed in this stock since inbreeding began, in 1921.[8]

Vaginal smears were made daily at about the same hour by means of a ball-tipped glass rod. The smears were stained with hematoxylin and eosin. In recording the results graphs were made designating O, estrus, the stage of cornification; M, metestrus, the stage of invasion by leukocytes; D, diestrus, the resting stage, and P, proestrus, the period in which the epithelial cells are nucleated and cornified (charts 1, 2 and 3). Secretion of estrogenic substance is denoted by the P and O stages only.

Experiment 1.—Although it has been demonstrated previously that the length of the period of heat is roughly proportional to the amount of estrogenic substance secreted, a preliminary experiment was performed to confirm this observation.

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6. Harde, E.: Influence des hormones et des vitamines dans la production des adéno-carcinomes mammaires chez la souris, Compt. rend. Soc de biol. **116**: 999, 1934.

7. Murray, W. S.: The Breeding Behavior of the Dilute Brown Stock of Mice (Little Dba), Am. J. Cancer. **20**:573, 1934.

8. Murray, W. S., and Little, C. C.: The Genetics of Mammary Tumor Incidence in Mice, J. Genetics **20**:466, 1935.

Six ovariectomized female albino mice 8 months of age were given injections as follows: One received 100 mouse units of theelol [9] in oil, one received 500 mouse units and one received 1,500 mouse units. Of the remaining three, each received 12 mouse units of theelin in aqueous solution. In the first three estrus was established in seventy-two hours and lasted for five, four and five days, respectively. Of the latter three, two failed to respond and seventy-two hours after injection one exhibited full estrus, which lasted twenty-four hours.

Thus, a prolonged period of heat represents a relatively large amount of estrogenic hormone liberated, whereas a short period is indicative of a small amount. However, among several animals each exhibiting prolonged periods it appears that there may be a wide variation in the amount of hormone liberated.

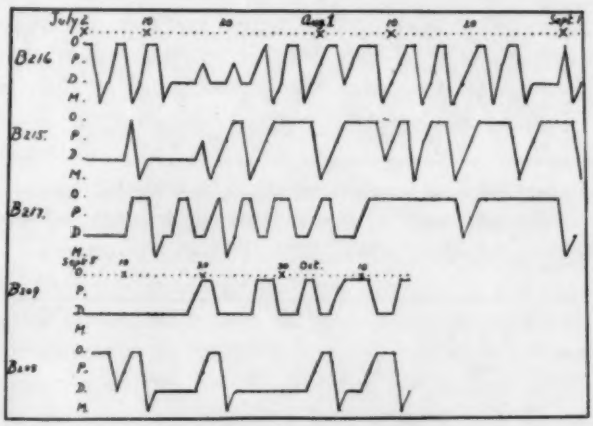

Chart 1.—Black mice of a noncancerous strain. The total number of days was two hundred and seventy-one, of which one hundred and thirty-nine (51.2 per cent) were spent in heat.

TABLE 1.—*Estrus Cycles in Three Groups of Mice*

Animals*	Total Number of Days Observed	Number of Estrus Cycles	Average Length of Cycle, Days	Percentage of Time in Heat
Group 1, five black mice, noncancerous strain	271	41	6.6	51.2
Group 2, three dilute brown cancerous strain, noncancer bearing	189	37	4.9	40.7
Group 3, five dilute brown cancerous strain bearing carcinoma of the breast	215	34	5.9	32.5

* All mice were approximately 1 year old.

Experiment 2.—The comparison of the estrus cycles in the three groups of mice described are summarized in the table.

Experiment 3.—In the final experiment three mice bearing carcinoma of the breast were ovariectomized and vaginal smears were made daily

9. The theelol was supplied by Parke, Davis & Co.

for one month, beginning one week after operation. No estrus periods were noted during this time; the smears all exhibited characteristics of the diestrus, or resting state.

COMMENT

An analysis of the data given in the table shows that in the small group of animals studied (of carefully controlled heredity) the average

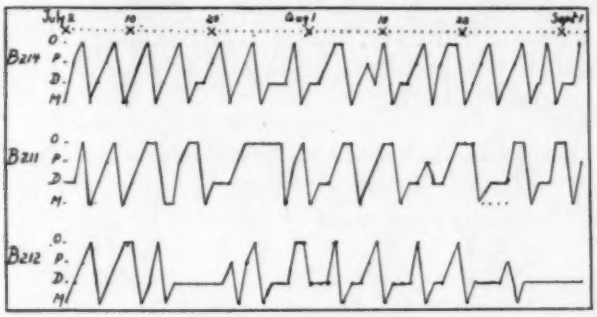

Chart 2.—Brown mice of a cancerous strain, but without cancer at the time of observation. The total number of days was one hundred and eighty-nine, of which seventy-seven (40.74 per cent) were spent in heat.

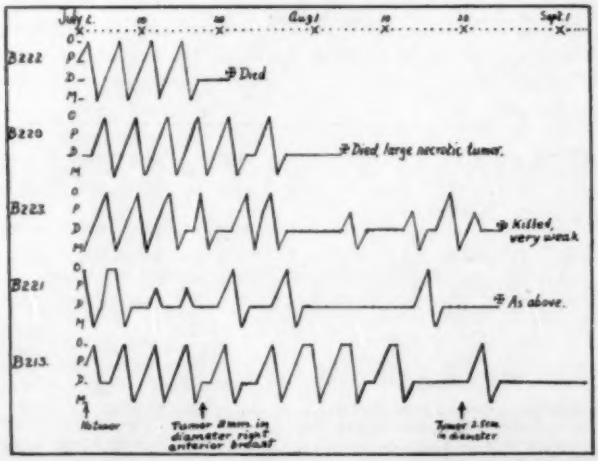

Chart 3.—Brown mice of a cancerous strain, bearing cancer at the time of observation. The total number of days was two hundred and fifteen, of which seventy (32.56 per cent) were spent in heat.

estrus cycle in the noncancerous strain was longer than that in the cancerous strain. The percentage of time in heat (flooding of the organism by estrogenic hormone) was also somewhat greater in the noncancerous strain. The latter observation may be partially explained by the fact that toward the end of the periods of observation in the cancer-bearing

animals the increasing size of the tumor affected the general health, and it is well known that estrus tends to be inhibited in animals that are not in good condition.

Thus, in these observations, no evidence was obtained of chronic hypersecretion of estrogenic hormone as a cause of spontaneous carcinoma of the breast in mice.

These results are in accord with those recently reported by Bonser,[10] who also compared the estrus cycles in mice belonging to strains of high and low incidence of carcinoma. This author did not differentiate between those mice of the former strain actually bearing tumors and those not bearing tumors. It was found that the average length of the cycles differed only by one tenth of a day and that the periods of heat averaged two tenths of a day longer in the strain in which the incidence was low. This author further showed that in ovariectomized mice of these strains, injections of estrogenic substances provoked a slightly greater response in animals belonging to the strain in which the incidence of carcinoma was low.

Loeb [11] and Cori [12] showed that the incidence of cancer of the breast in female mice belonging to a strain in which the incidence of carcinoma was high was greatly reduced if ovariectomy was performed at a very early age and that the incidence was not affected if this operation was performed after the eighth month of life. Since spontaneous carcinoma rarely if ever develops in immature breasts, it would appear that the rôle of the ovaries in the development of carcinoma of the breast is secondary, in that ovarian secretion is necessary for the development of the mammary gland to an adult stage, after which malignant neoplasia may occur.

Thus, the demonstration by Lacassagne and Burrows that estrogenic substance in large doses may cause carcinoma of the breast in male mice might well be interpreted as a demonstration of malignant degeneration resulting from the subjection of a tissue over long periods to a strong extraneous specific growth stimulus (estrogenic substance acting on the mammary ducts). It is not apparently a demonstration of the natural mechanism for spontaneous malignant degeneration in the mammary glands of mice.

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10. Bonser, Georgiana: A Comparison of the Normal Oestrous Cycle and of the Response to the Administration of Oestrin in Two Strains of Mice Differing Greatly in Incidence of Spontaneous Mammary Cancer. J. Path. & Bact. **16**:33, 1935.

11. Loeb, L.: Internal Secretion as a Factor in the Origin of Tumors, J. M. Research **40**:477, 1919.

12. Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas of Mice, J. Exper. Med. **45**:983, 1927.

SUMMARY

Because injections of large doses of estrogenic hormone have been shown to cause mammary carcinoma in male mice (Lacassagne, Burrows), comparisons are reported between the estrus cycles in female mice belonging to a strain of high incidence of mammary carcinoma and those in females of a noncancerous strain in order to determine whether in the former strain a hypersecretion of the ovary exists to explain the high incidence of cancer of the breast. In the animals studied the periods of heat (period of secretion of estrogenic hormone) were somewhat longer in the animals belonging to the noncancerous strain than in those of the cancerous strain, whether or not they exhibited tumors of the breast. This constitutes evidence against the hypothesis that an excess of secretion of estrogenic hormone by the ovary plays the principal etiologic rôle in spontaneous mammary carcinoma in mice.

A REVIEW OF UROLOGIC SURGERY

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(*Concluded from page 348*)

PROSTATE GLAND

Hypertrophy.—Teem [36] reviewed 733 consecutive necropsies which were performed in the years 1930 to 1933, inclusive, at the Mayo Clinic, on male patients who were more than 40 years of age. Of these men, 334 (45 per cent) had prostate glands which were larger than normal. The purpose of the investigation was to make a comprehensive study of the gross anatomy of the prostate gland and of the microscopic anatomy of the testis in a large series of cases. It was thought that thorough correlation of the findings in examinations of subjects of all decades of life and, consequently, of prostate glands of all sizes might give some information on the tissue in the testis concerned with the development and maintenance of the prostate gland. Such a study was undertaken, therefore, on the premise that it would be possible to determine from the histologic appearance of a tissue some idea of its function, particularly in the elaboration of an internal secretion. Of the 504 prostate glands studied, 301 were classified as normal, 189 as hypertrophied, and 14 as not as large as normal either in weight or in dimensions.

36. Teem, M. van B.: The Relation of the Interstitial Cells of the Testis to Prostatic Hypertrophy, J. Urol. **34**:692 (Dec.) 1935.

The interstitial cells of the testis are numerous at birth, reach their greatest average relative number between the ages of 10 and 19 years, and then gradually and progressively decrease in number as age advances. The decrease in the average relative numbers of interstitial cells in subjects who have hypertrophied and those who have normal prostate glands is about parallel until the age of 69. After that age, the average relative number of interstitial cells among subjects who have hypertrophied prostate glands decreases more rapidly than does that among subjects who have normal prostate glands. A remarkably good state of preservation of the seminiferous tubules and of spermatogenesis was not infrequently encountered between the ages of 40 and 89. Tumor of the interstitial cells of the testis may be associated with a normal or a subnormal size of the prostate gland.

Hemorrhage.—Shivers [37] said that severe hemorrhage of prostatic origin, which requires emergency treatment, appears to be rare since only 26 cases have been reported in the literature. In 15 cases it was necessary to enucleate the prostate gland to save the patient's life. In 7 cases reported in the literature and in a case that Shivers observed suprapubic drainage did not control the hemorrhage. The cause of the prostatic ulceration in the latter case was not found but was undoubtedly a significant factor in producing the primary hemorrhage. Emergency prostatectomy is not desirable if any other method can be used to control the bleeding. This is particularly true when renal or cardiovascular disease is present. Instrumentation in this type of prostate would be an important factor in inducing a severe hemorrhage. If the vessel is accessible, cauterization of the bleeding point may stop the hemorrhage. If the bleeding cannot be otherwise controlled, enucleation of the prostate gland is proper.

Resection.—Davis [38] reported 748 cases in which transurethral resection of the prostate gland was performed. In his opinion any type of prostate gland may be treated by resection provided the operator has the skill and the perseverance to continue until a satisfactory operation has been consummated. It is generally conceded that resection is suitable in cases of obstruction by bars, contractures or small median and lateral lobes of the gland. When the operator has acquired sufficient skill, the large lateral lobes can also be adequately removed. Two sittings may be necessary for resecting large lateral lobes, although Davis prefers to complete each resection at one operation. From 50 to 75 Gm. of tissue have repeatedly been removed within one and a half hours.

37. Shivers, C. H. de T.: Uncontrollable Hemorrhage from Benign Prostatic Enlargement: Report of a Case, J. Urol. **34**:417 (Nov.) 1935.

38. Davis, T. M.: Transurethral Prostatic Resection with Report of Seven Hundred and Forty-Eight Cases, South. M. J. **28**:693 (Aug.) 1935.

An operation of this duration is not any more exhausting to the patient than are two operations of shorter duration. In the two stage operation there is less hemorrhage during the second stage, and, as the lobes have a tendency to collapse toward the midline, removal of tissue is expedited.

If the residual urine measures more than 5 ounces (148 cc.), adequate preliminary preparation is significant. Decompression by means of an indwelling urethral catheter is the method of choice. It has never been necessary or desirable, in Davis' experience, to employ suprapubic cystotomy in the preparatory treatment. When this is done, prostatectomy should be the method of choice, except when there is malignant growth. Vasectomy is not necessary. In this series of 748 cases there were 14 instances of preoperative epididymitis and 21 of postoperative epididymitis. Vasectomy in each of these 748 cases would have subjected too many patients to a needless operation.

When obstruction is caused by a median bar, excision of the bar is sufficient to insure permanent results. If there is enlargement of the median lobe of the prostate gland, the entire median lobe should be removed. If there is hypertrophy of the lateral lobes, at least two thirds of the lateral lobes should be removed. In many cases the lobes are removed to the muscles or the supposed capsule. The anesthesia preferred is caudal and transsacral block anesthesia produced with 1 per cent solution of procaine hydrochloride. It is safe, of sufficient duration and free from undesirable sequelae. In the occasional case in which this anesthesia is not complete, a special needle adapter for the sheath of the resectoscope, which permits the prostate gland to be infiltrated under vision, is used. The improved Davis-Bovie generator produces a cutting current that can be adapted to the particular type of prostate gland that is being resected. The current may be varied from one that sections tissue as well or better than the tube machine with a thin depth of dehydration to one that sections tissue with a zone of dehydration that controls all except the largest arteries. The advantages of these currents are that they permit the resection of fibrous or vascular glands with equal facility and minimal hemorrhage. Sectioning with the McCarthy resectoscope is toward the operator, and when the capacity of the bladder is 8 ounces (236 cc.) or more, repeated sections should be made, and the tissue allowed to fall into the bladder. Hemorrhage rarely interferes with vision until the entire lobe is removed. When the capacity of the bladder is reached, the water is allowed to return through the sheath, and the tip of the sheath is wiggled near the base of the bladder. Many, if not all, of the sections of tissue will come out through the sheath. Bleeding vessels are controlled, and any remaining obstructing tissue in the lobe is removed.

Hemorrhage should be completely controlled in each lobe before removal of tissue from another lobe. If there is median obstruction

of the gland, the tissue is removed to permit an unobstructed view from the verumontanum to the trigon. When one is removing this type of obstruction there always appears to be obstructing tissue at the posterior cut edge. Within the bladder the lateral lobes are removed so that they will be on a level with the walls of the bladder. Within the urethra the lateral lobes are excavated laterally. When the view is from the level of the verumontanum there should be a concavity with the narrow points at the vesical orifice and on a level with the verumontanum. Hemorrhage should be completely controlled before the patient leaves the operating table. All vessels should be coagulated by moving the loop backward and forward over the area. A certain amount of bleeding may have to be tolerated at the apex of the gland, near the external sphincter. This is usually produced by trauma and will subside of itself when the sheath is removed and the catheter is in place. Coagulation in this area is likely to result in damage to the sphincter and must be avoided.

The patient should be kept quiet for forty-eight hours. The retention catheter should be connected to a rubber tube which is connected to a bottle at the bedside. The catheter should then be irrigated by a nurse, when necessary, using cold sterile water with a plunger syringe, suction being employed to remove any clots. Irrigations should be continued until the drainage is clear, a period of usually not more than twenty-four hours.

No difficulty has been experienced with immediate postoperative hemorrhage. It is Davis' opinion that the majority of the reported difficulties have resulted from the use of improper coagulating current or from insufficient care in coagulation; others have resulted from a fall in blood pressure during the operation and a rise several hours afterward. Serious infection has been negligible in this series of 748 cases. The urine contained pus cells for about two months after operation. If the bladder is able to empty completely or if the amount of residual urine is not more than 1 ounce (30 cc.), the infection will clear spontaneously. If sufficient tissue is not removed and obstruction continues, the infection will persist. There were 2 instances of permanent incontinence in the 748 cases: one that was intentional in a case of carcinoma, and the other in a case of benign hypertrophy with injury in the region of the sphincter. In the seven and a half years during which resection of the prostate gland has been used by Davis, 46 patients who had had their prostate glands removed within five years were operated on by resection. Twenty-four of the 748 patients in this series required subsequent resection; 9 of these were operated on within the first six months; 7 who had benign obstruction had a definite recurrence; 8 who had malignant obstruction required one or more resections for continued relief.

Resection of the prostate gland when properly performed has a low mortality. In a series of 416 cases in which resection was done there were no deaths; in another series of 332 resections there were 6 deaths, making a mortality of 0.8 per cent in the total of 748 cases.

Thompson [39] said that until a few years ago urologists agreed that litholapaxy should be employed only when there was no other condition within the bladder requiring operation; hence practically all patients with prostatic enlargement and coincident vesical calculus were subjected to suprapubic operation. As a general rule, this was done in two stages, and the patient therefore spent a long time in the hospital. The development of transurethral prostatic resection has enabled the urologist to remove the offending prostate gland as well as any stones that are present in one operation, thus greatly shortening convalescence. Thompson reports 54 cases in which he has employed this combined procedure. The amount of prostatic tissue which was removed varied from 3 to as much as 47 Gm. The calculi in some cases were as large as 5 cm. in diameter. The incidence of epididymitis, chills and fever and the mortality were no greater in these cases than in similar cases in which prostatic resection only was employed.

Ballenger [40] said that in more than 400 cases in which resection of the prostate gland was done the mortality was about a tenth of what would have been expected if prostatectomy had been performed in the same cases. Many of the patients have been regarded as altogether unfit for prostatectomy if it had been required. He has performed prostatectomy on only 2 patients since he began to use resection of the prostate gland. He seldom performs suprapubic cystotomy; transurethral resection has been found safer than cystotomy, even when the prostate gland is large and has to be removed in two stages. While this may increase the mortality from resection, it will also increase the number of patients who are alive after the employment of relief measures for obstruction of the prostate gland.

Wesson [41] stated that the time to control hemorrhage in resection of the prostate gland is while the patient is anesthetized at the time of operation. He prefers the Herbst bag for this purpose and uses the spark as little as possible, thereby preventing pyelitis. The resection is continued until the bleeding becomes annoying; then the sheath is removed, and the Herbst bag is introduced on a stylet. The end of the catheter is passed through a rubber sponge, the bag is inflated, and the pressure is maintained for about seven minutes. When the sheath

39. Thompson, G. J.: Simultaneous Litholapaxy and Prostatic Resection, Proc. Staff Meet., Mayo Clin. **10**:689 (Oct. 30) 1935.

40. Ballenger, E. G., in discussion on Davis,[38] p. 699.

41. Wesson, M. B., in discussion on Davis,[38] p. 699.

is reintroduced, any bleeding will be from large vessels that can be easily seen and fulgurized.

Davis' treatment of the sphincters is anatomically sound. It should be borne in mind, from the urinary standpoint, that the prostate gland is the neck of the bladder, that is, two surgical sphincters that have been invaded by prostate tubules. A sphincter is a muscle whose origin and insertion is in itself. Hence, the external sphincter of the bladder that surrounds the apex of the prostate gland is a true anatomic sphincter of striated muscle fibers. The so-called internal sphincter is a surgical and not a true anatomic sphincter and is composed of smooth muscle fibers. It is not a circular loop but is composed of two arcs of muscles that interlock and close the bladder by a tonsillotome-like action. The fibers of the external longitudinal layer of the bladder, when they reach the vesical orifice, sweep upward and pass over the top, forming a heavy loop or bundle. The inferior arc is composed of fibers from the internal circular layer. They form an oblique loop with one end in the floor of the vesical orifice and the other above the verumontanum. In prostatic resection, laterally and posteriorly, the superficial part of the weaker loop, which is composed of the fibers from the circular layer, is removed along with the hypertrophied gland. The powerful superior arc or bundle, which is situated anteriorly, is protected by not cutting in that sector.

Collings [42] said that certain limitations of transurethral operations must be recognized. Relief has been secured in from 90 to 95 per cent of 75 cases occurring during the last two years in which obstruction of the prostate gland was removed with the knife electrode. Four deaths occurred, in cases in which there was carcinoma of the prostate gland. He has traced 135 patients who were operated on between 1923 and 1933; 16 died within from one month to five years after operation, 6 of heart disease, 3 of pneumonia, 2 of carcinoma of the prostate gland and uremia, 3 of septicemia or pyemia, and 1 of typhoid fever; 1 committed suicide. Of the 119 patients who are living, 77 per cent obtained complete relief, and 23 per cent had some urinary frequency and burning at times. The excision of the prostatic urethra with the knife electrode has given maximal relief with few complications or operative deaths.

Thompson [43] reported that 49 of 1,694 patients subjected to transurethral resection at the Mayo Clinic between Jan. 1, 1913, and Jan. 1, 1935, were again operated on for the relief of urinary obstruction;

42. Collings, C. W.: Endoscopic Excision of Prostatic Obstruction, J.Urol. **34**:396 (Nov.) 1935.

43. Thompson, G. J.: Recurrence of Urinary Obstruction Following Transurethral Prostatic Resection, J. Urol. **34**:405 (Nov.) 1935.

16 of these 49 patients originally had carcinoma of the prostate gland, 10 a median bar or a contracture of the vesical neck, and 23 an adenomatous enlargement of the type formerly treated by prostatectomy. The 10 patients with a median bar or a contracture of the vesical neck belonged to the group for which the punch operation is recognized to be the operation of choice; symptoms of urinary obstruction recur in a larger proportion of patients of this type than of those with adenomatous enlargement of the prostate. The 23 patients with adenomatous hyperplasia probably all had a certain amount of regrowth of prostatic tissue, although 6 of them reported that they had not been completely relieved by the first operation; in 5 others, definite new growth could be recognized by cystoscopy. In each instance in which there was a recurrence, the stay in the hospital following the second operation was shorter than that after the primary operation; there were no complications. Recurrent obstruction of the urinary tract following transurethral resection will be infrequent in cases in which the primary operation is thorough; if a good functional result is not immediately obtained, it is best to remove more tissue without delay. More deformity of the prostatic urethra results from suprapubic or perineal prostatectomy than from prostatic resection; recurrent intra-urethral proliferation of adenomatous tissue is little, if any, greater after transurethral resection than after prostatectomy. Up to the present, the percentage of cases in which urinary obstruction has recurred after transurethral resection is much less than has been predicted.

PENIS

Carcinoma.—Barringer [44] abstracted from the records of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, the data in 100 cases of carcinoma of the penis. Sixty-three patients (less than two thirds of the series) apparently and probably had no lesion beyond the primary one of the penis. Fifty-five of these 63 patients have been free from symptoms for periods ranging between one and more than ten years following treatment. Eight patients died of the disease between one and five years after treatment, and 19 (19 per cent) have been well for more than five years.

Thirty-seven patients (more than a third of the series) had metastasis to the groin. In 9 (24 per cent) of these patients, the involvement was controlled for periods of from one to ten years. Radical dissection of the groin was not done by Barringer in any of these 9 patients. The 28 remaining patients died of carcinoma, although 4 lived between two and three years and 1 lived more than three years. Fifteen of

44. Barringer, B. S.: Inguinal Gland Metastases in Carcinoma of the Penis, J. A. M. A. **106**:21 (Jan. 4) 1936.

the 28 patients died within the first year. In 22 of the cases there was no microscopic examination of the lesion, while a positive diagnosis of carcinoma was made in 14 cases. In 5 of the 14 cases a positive diagnosis of carcinoma was made by the aspiration method. In 5 of the 9 cases in which the growth was controlled there was a positive pathologic diagnosis of carcinoma of the inguinal lymph nodes. In 3 cases no diagnosis was made, and in 1 case the diagnosis was questionable. Only 2 patients have lived free from symptoms for more than five years. In 4 patients metastasis occurred after treatment was started. In 10 of the 37 patients in whom there was metastasis to the lymph nodes there was infection of the involved lymph nodes. This resulted in the breaking down of the carcinoma into a sloughy ulcerated mass and eventually in the death of the patient. No known treatment can cope with such a situation. Six of the patients came to the hospital with lymph nodes which were infected and broken down, and in 4 others this condition developed while they were in the hospital. Elimination of an infected primary carcinoma of the penis should be rapidly done. This is generally accomplished by a cleancut operation, usually partial amputation of the penis 1 cm. beyond the carcinoma.

Two patients died of hemorrhage as the result of invasion of the femoral vessels by carcinoma. One patient died from the operation, which consisted of removal of the penis and extensive resection of the inguinal lymph nodes. This death was primarily the result of infection of the affected region, and the fact is a point in favor of control by irradiation rather than by operation.

Both operation and irradiation have to date proved impotent in dealing with metastases to the inguinal lymph nodes. Operation has probably been well done, and irradiation probably has been inadequate as to dosage and proper application. Surgical removal carries a definite mortality; irradiation, none. Early aspiration biopsy of the inguinal lymph nodes is imperative. If the lymph nodes are cancerous, a combination of external irradiation and implantation of radon seeds through an incision and under vision seems to offer the most satisfactory prognosis. Either one of these procedures alone seems to be ineffective for this type of growth. Primary external irradiation by the Coutard method, followed immediately by operative removal before dermal changes have taken place, may offer another lead toward cure.

Hypospadias.—Cabot,[45] in discussing plastic operations for hypospadias, said that, until relatively recent times, this type of deformity had not been completely overcome. Operation did not restore the affected

45. Cabot, Hugh, in discussion on Walters, Waltman: Plastic Operations on the Genito-Urinary Tract: II. Operations on the Urethra, Proc. Staff Meet., Mayo Clin. **10**:563 (Sept. 4) 1935.

parts to normal, and frequently a stricture or a fistula marred the result. There are three types of operation for the construction of the new urethra after the deformity of curvature has been corrected. The oldest of these is the so-called Thiersch-Duplay type, in which a skin flap is taken from the shaft of the penis and is therefore of thin pliable skin that does not bear hair. With experience, the results obtained with this operation are excellent, but there is risk that a fistula will form which may necessitate several operations in order to complete the work. In the Bucknall operation, fistula and stricture are avoided. The principle involved is that of turning down the penile portion against the scrotum, thereby obtaining a satisfactory flap with a broad pedicle. The objection to this procedure is that it utilizes for the floor of the urethra the tissues of the anterior portion of the scrotum, which are hair-bearing. The Ombrédanne operation has the same advantages as the Bucknall technic, although not to the same extent. It also utilizes the hair-bearing tissues of the midportion of the scrotum, and therefore it may have the same disadvantage. It is interesting to note that there is no long-time follow-up evidence in regard to the ultimate results of these operations. Most of the reports have been on patients who were followed only a relatively short time after operation, and these reports cannot be regarded as complete evidence as to success.

It is not sufficiently realized that the traumatic stricture differs essentially from the so-called inflammatory stricture, which is commonly the result of a gonorrheal infection. As compared with the inflammatory stricture, the traumatic stricture contracts early and fiercely and is exceedingly difficult to dilate. Cabot expressed the belief that the traumatic stricture, if it has not been treated skilfully and successfully by accurate reunion of the divided ends at the time of injury, should always be treated by resection and anastomosis. The important fact to consider is that there is a free and segmental blood supply of the corpus spongiosum. This structure does not resemble the corpora cavernosa by being seriously damaged if the supply of blood is interfered with at the base. The corpus spongiosum can be safely mobilized with its contained urethra to almost any extent which is necessary to make possible union between the divided ends without tension. The avoidance of tension is the crux of the procedure, and mobilizing the anterior end is the significant feature of the operation. The only other important point is that the suture should be begun on the roof. This region having been securely united, the floor of the canal should be slit, if possible, in both segments, although it is necessary to slit it only in the anterior segment, since the posterior segment will commonly be dilated. This enables union to be made, giving a canal of a caliber much in excess of the normal. When this circular scar

contracts, the ultimate result should be a canal of normal caliber. Essential features of the operation are thorough exposure, complete removal of the stricture and the surrounding scar tissues, union of the ends without tension, and provision that the canal will at the time of operation be considerably larger than normal.

URETHRA

Injuries.—Delzell and Stevens [46] presented a study of 37 cases of rupture of the urethra. In 7 cases the rupture involved the penile urethra; in 21, the bulbous portion; in 2, the membranous portion, and in 2, the prostatic urethra. In 7 cases the rupture was the result of injury to the penis; in 2, of a gunshot injury; in 19, of a straddle injury without pelvic fracture, and in 9, of straddle injury associated with fracture. Important diagnostic and therapeutic problems relate to prompt institution of drainage to control infection and to lessen the formation of scar tissue, early repair of the rupture when conditions permit and close observation of the patient in the hospital when the diagnosis or the procedure is in doubt. Six patients died, 1 of pneumonia twenty-five days after operation and 5 of sepsis. Three of the patients who died of infection were not seen until late.

Martin [47] divided injuries of the urethra into the following four classifications: (1) the so-called straddle injury, in which the membranous urethra is wholly or partially severed; (2) the classic rupture of the bladder produced by moderate impact over the organ when distended; (3) instrumental rupture of the bladder or of the posterior urethra, and (4) the injury, especially that of the posterior urethra, produced by a crushing force or a violent impact sufficient to cause fracture of the pelvis.

While the incidence of fracture of the pelvis is relatively high, only in a comparatively small percentage of the cases is the condition complicated by injury of the urethra or bladder. When such an injury is present, it is important to recognize it early and institute surgical measures for the purpose of drainage, so as to prevent further leakage into surrounding tissues. If there is any doubt as to the extent of the injury, drainage should always be instituted. In every region where urinary leakage may seem to be present or where it is even suspected to be present, adequate drainage should be provided. Unnecessary drainage leads to no serious results unless severe shock is present. If shock is excessive, it is probably the result of injuries concomitant with the urethral injury.

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46. Delzell, W. R., and Stevens, A. R.: Traumatic Rupture of the Urethra: Study of Thirty-Seven Cases, J. Urol. **34**:372 (Nov.) 1935.

47. Martin, H. W.: Injuries of the Posterior Urethra, J. Urol. **34**:718 (Dec.) 1935.

The treatment consists of ample drainage of the bladder and of every region where urine may have leaked into the tissues. In many instances, infection of the urine has existed previous to the injury. Extravasation of urine invariably leads to serious infection through necrosis of the tissue. A midline abdominal incision is made over the hypogastrium. It is seldom justifiable to explore the peritoneal cavity unless there is definite evidence of injury to abdominal viscera. The bladder is opened suprapubically. The prevesical region should be examined; after opening the bladder as high up toward the retracted peritoneal fold as possible, the inner wall should be thoroughly palpated for evidence of rupture. If tears exist, better exposure may be needed. If not, a Gutierrez retrograde staff should be introduced through the suprapubic opening into the vesical neck and out through the prostatic urethra into the bulbous urethra; an incision is made in the perineum over the tip of this retrograde staff. The staff is then pushed through this buttonhole opening in the perineum, and a rubber catheter or a piece of rubber tubing the size of a no. 22 French catheter is pushed well over the tip of the staff like a sleeve; it is then encircled and fastened on the staff with a silk ligature, tied securely. The staff is then withdrawn, carrying the rubber tube from the perineum into the bladder and up through the suprapubic incision in the bladder on to the skin, where it can be visualized. The rubber tube is released from the tip of the staff and is transfixed with heavy twisted silk, size 12 or 14, and the silk is knotted to form a loop. The rubber tube is then withdrawn by pulling on the portion still projecting in the perineum until the upper end is resting on the trigon, or the upper end of the tube may be sutured to the edge of the skin of the suprapubic incision. The silk loop is then fastened with a silk suture thread to the skin of the abdominal incision. A suture through the tube into the skin at one edge of the perineal wound will hold it firmly in place. A de Pezzer catheter, no. 22 French, is then sutured in place for drainage of the bladder. If there is any ecchymosis or tumefaction of the perineum, scrotum or shaft of the penis, it should be liberally incised as in any case of extravasation of urine.

Stricture.—Stevens [48] said that ectopic kidneys are not uncommon in women. The ectopia is sometimes responsible for symptoms suggestive of pathologic changes in the generative tract. Pyelography is of value in the differential diagnosis of pathologic conditions of the female generative and urinary organs. Urethral stricture occurs frequently in women. In the majority of cases it is situated at the external meatus. It may be congenital or acquired. Frequently it is

48. Stevens, W. E.: Some Observations on Female Urology, Tr. Am. A. Genito-Urin. Surgeons **28**:377 (June) 1935.

responsible for pathologic changes in the upper part of the urinary tract and for a large variety of subjective symptoms, including pain in various situations. The average size of the normal urethra of the adult female is that of a no. 26 French; the average size in the presence of urethral stricture is that of a no. 21 French. Urethrograms show the angular bend and narrowing of the normal female urethra. Urethrography is a valuable diagnostic procedure. Frequently it is indicated in the presence of symptoms suggestive of pathologic changes in the urinary tract in this sex.

TESTES

Tumors.—Smith, Dresser and Mintz [49] reported a series of 100 cases of tumor of the testis the data on which were collected from a number of hospitals about Boston. The highest incidence of teratoma was in persons between the ages of 20 and 30 years; that of embryonal carcinoma was in those between 30 and 40 years. Between these two groups there was no marked difference in the rate of progress of the disease. A definite history of trauma was obtained from 13 per cent of the patients; in 5 per cent the uninvolved testis was or had been incompletely descended. There were 3 cases of bilateral tumor. Fifteen per cent of the patients were apparently well two or more years after orchidectomy. Of these, 6 had not been irradiated. In only 1 of the well patients had metastasis been noted. To the extent of the authors' knowledge, all patients who had metastatic involvement when irradiation was instituted, died of the disease or still have metastatic involvement. Only 40 per cent of the patients in this series were adequately irradiated. A standard should be established for roentgenotherapy following orchidectomy. It is necessary to irradiate the entire abdomen inasmuch as the most frequent site for metastasis is in the lumbar chain of lymph nodes. If the thorax is not included in the first series of treatments, diagnostic roentgenograms should be made every two months for at least two years.

Cutler and Owen [50] reported the results of quantitative determinations of the follicle-stimulating hormone in the urines of 66 patients who had teratoma of the testis. The amounts varied between 50 and 16,000 mouse units per liter. The amounts excreted in the urines of 13 normal males who had benign lesions of the testis were less than 50 mouse units per liter. The evidence supports the view that patients with teratoma of the testis excrete more than 50 mouse units per liter of urine, a fact which gives a diagnostic value to the determination of

49. Smith, G. G.; Dresser, Richard, and Mintz, E. R.: Radiation Treatment of Tumors of the Testicle, J. Urol. **34**:462 (Nov.) 1935.

50. Cutler, Max, and Owen, S. E.: Clinical Value of Prolan A Determinations in Teratoma Testis, Am. J. Cancer **24**:318 (June) 1935.

this hormone. Usually, a marked diminution in the excretion of the hormone following irradiation is accompanied by a marked regression of the disease and an improvement in the general condition of the patient; failure of the excretion to diminish or an increase following treatment is paralleled by failure to respond to therapy. Local recurrence of teratoma is often preceded by a rise in the hormone in the urine, rendering the determination of the hormone of value in the follow-up control of this group of patients. The total output of urine for twenty-four hours should be determined and taken into consideration when the quantitative determination of the hormone is made under conditions in which clinical conclusions are to be based on small variations, in order to avoid errors that might arise owing to differences in the intake of fluids. A modification of the benzoic acid method described by Katzman and Doisy is presented. This renders the test more accurate when the quantities of the excreted hormone are small, and this modification is preferable when the urine contains toxic products.

Fortner and Owen [51] said that chorionepithelioma rarely occurs in males, although many cases of the tumor in women have been reported. While no positive statement can be made at present concerning the origin of chorionepithelioma, there are many facts to be considered. From a study of the tumor in the female, the trophoblast is known to be normally an invasive type of tissue, and chorionic cells are reputed to possess the property of digesting the maternal tissues. The embedding of the ovum is thought to be accomplished by the aid of this characteristic. The cells of the trophoblast are endowed with marked capacity for growth. Trophoblastic emboli are said to occur in 80 per cent of normal pregnancies. This parasitic tissue, then, is able physiologically to invade and wander. The formation of chorionepitheliomatous tissue in the male has been regarded as evidence of a metaplastic change in an embryonal ectodermic structure which, under certain unrecognized conditions, is capable of producing this variety of tumorous tissue, just as these tissues may undergo carcinomatous changes in response to other stimuli.

The biologic assay of the urine for the hormone that stimulates the follicle offers the possibility of timely diagnosis. Chorionepithelioma of the testis is associated with a urinary ouptut of this hormone varying from 10,000 to 150,000 mouse units per liter. Teratoma is also associated with an excretion of excessive amounts of this hormone in the urine, but the quantities range from 50 to 10,000 mouse units per liter, depending on the type of tumor. Since normal urine of a male

51. Fortner, H. C., and Owen, S. E.: Chorionepithelioma in the Male, Am. J. Cancer **25**:89 (Sept.) 1935.

contains less than 50 mouse units of the hormone per liter, an increase in the amount furnishes a diagnostic test for chorionepithelioma of the testis.

Since the tumor consists of anaplastic and undifferentiated tissue, it may be expected to be highly radiosensitive. After the diagnosis has been made, preoperative irradiation may be followed by radical surgical removal of the primary growth, with subsequent postoperative irradiation to the primary site. For metastatic involvement, irradiation is at present the treatment of choice. There is a possibility that treatment of the tumor may eventually be nonsurgical, and consist in injections of serum or in endocrine gland therapy. In view of the observations made by Fraenkel, it seems that serum of pregnant animals may be beneficial. Such serums are now being utilized, but it is too early to form accurate conclusions. Owing to the close association of teratoma of the testis with chorionepithelioma, as evidenced by their endocrine relationship, it may be that the lytic agents occurring in the serum during pregnancy also affect the teratoma, a problem which is worthy of further investigation.

Two cases of chorionepithelioma of the testis are presented, with gross and microscopic illustrations. Sections from the primary tumor and from metastatic nodules disclosed in both these cases characteristics typical of chorionepithelioma. In addition to the syncytial masses dipping into large regions filled with erythrocytes, some strands appeared to have central connective tissue cores with capillaries, resembling chorionic villi. Sections through the mammary glands presented an increase in the number of acini, with an increase in the amount of fibrous tissue between them. The acini were moderately dilated and displayed evidence of activity.

Ferguson [52] said that a study was made in 1931 of the effect of various technics for administering a divided dosage of roentgen rays in the treatment of teratoma testis. The treatment of a series of patients with metastatic teratoma of the testis was begun as follows: The abdomen was divided into three anterior portals on the affected side. Two posterior portals were used. The groin and scrotum were treated separately. The factors used were a target skin distance of 70 cm., 200 kilovolts, 200 milliamperes, 0.5 mm. of copper and 1 mm. of aluminum. A dose of 400 roentgens was delivered to each portal in rotation on successive days. The total dose delivered in each instance was 2,000 roentgens to each skin portal. From April 1, 1932, to April 1, 1934, 25 patients were treated by this technic. During the same period, 27 patients who had the tumor were treated with roentgen

52. Ferguson, R. S.: Selective Irradiation in the Management of Teratoma Testis, J. Urol. **34**:458 (Nov.) 1935.

radiation by the full erythema technic or with other agents. From the clinical standpoint each group of patients represented the average patient with teratoma of the testis seen at the hospital, and the treatment of one group was not less difficult than that of another. Of the 25 patients treated with the divided doses, 12 (48 per cent) were alive and without evidence of disease on April 1, 1935. In the other group, 10 (37 per cent) were alive and without evidence of disease for from one to three years.

The character of the growths in the patients in whom the clinical results were satisfactory was investigated. It was found that an increased percentage of growths formerly thought to be radioresistant had been observed in the patients cured with divided doses. Comparison was made with the cured patients in the series of 154 who were subjected to the full erythema doses.

The conclusion was that a further increase in the target skin distance and in filtration and a further division of the dose with the attainment of a higher total dose should be selected as the treatment of choice for the more radioresistant types of teratoma. It was also evident from the study of the series of 154 cases that intensive irradiation with less filtration and larger daily doses was preferable for the more sensitive types of the tumor. Consequently, the technic of external irradiation may be selected on the basis of the structure of the tumor and its biologic behavior. In 1933 it was shown that the biologic response of the teratoid tumor to irradiation, as measured by the quantitative assay of the urine for the follicle-stimulating hormone, is a more reliable index of the radiosensitivity of the tumor than the histologic structure alone. When the structure of the growth or its biologic response to previous treatment is known a fairly accurate prediction of radiosensitivity or resistance may be made. The patients with sensitive teratoma are now being treated by Ferguson by the 70 cm. technic, but those with more resistant teratoma are being treated by prolonged irradiation with smaller doses, greater distance and heavier filtration. Early results indicate the wisdom of this selection of treatment.

Ferguson summarized his findings as follows: The more radioresistant the tumor, the greater the necessity for more prolonged, less intense irradiation. Conversely, the more sensitive the tumor, the greater the necessity for intensive irradiation.

Undescended Testis.—Wangensteen [53] reported observations demonstrating spermatozoa in the semen after bilateral orchiopexy for failure of complete descent of the testes. He also presented proof of complete spermatogenesis in seminiferous tubules of such a testis. In pigs with

53. Wangensteen, O. H.: The Undescended Testis: Its Fate After Satisfactory Scrotal Anchorage, Ann. Surg. **102**:875 (Nov.) 1935.

retained testes which could be brought into the scrotum by orchiopexy, spermatogenesis was also demonstrated. It is apparent, however, in human beings as well as in pigs in which this deformity has been corrected, that satisfactory scrotal anchorage does not permit a uniform and diffuse restoration of mature germinal epithelium such as attends scrotal transference of the normal (dog's) testis, temporarily elevated from the scrotum to the abdomen.

Whereas these results scarcely justify a stockbreeder in having bilateral orchiopexy performed, for breeding purposes, on an animal with a valuable pedigree, the virtue of orchiopexy in rectifying the sterility of cryptorchides warrants the performance of the operation in man in all suitable cases in which the condition is bilateral. Apart from the consideration of sterility, which does not concern unilateral failure of descent, the same indications which determine the necessity for operation in cases of bilateral undescended testis should be applied in cases of unilateral retention of the testis.

Pace [54] examined 24 specimens of unilateral undescended testis from adults. These organs had been removed surgically within the past thirty-two years at the Mayo Clinic. Seven of the specimens had been situated in the right inguinal canal; 7, in the left inguinal canal; 4, at the left external abdominal ring; 2, at the right external abdominal ring, and 3, within the abdomen, 2 on the left side and 1 on the right. Twenty-two of these undescended testes were associated with inguinal hernias. Two patients were in the second decade of life; 6, in the third decade; 5, in the fourth decade; 4, in the fifth decade; 2, in the sixth decade, and 5, in the seventh decade. One of the 2 testes obtained from patients in the second decade of life contained tubules which were not devoid of germinal epithelium and might have produced a mature germinal epithelium if placed in the scrotum. The testis of the other patient in this decade of life contained only remnants of testicular tissue and probably was grossly undeveloped. Each of the 6 specimens from patients in the third decade of life revealed some evidence of atrophy of the germinal epithelium; in each instance the remaining epithelium was in a fair state of preservation and might have given evidence of regeneration if the testis had been placed in its normal position. After histologic study of the 5 specimens obtained from patients in the fourth decade of life, it appeared that 4 might have been able to produce a mature germinal epithelium if they had been placed in the scrotum. Of the 4 specimens from patients in the fifth decade, the epithelium in 2 might have functioned had the testes been placed in the scrotum. In 1 of the 2 patients in the sixth decade of life, the

54. Pace, J. M.: The Histologic and Pathologic Anatomy of the Retained Testis, Proc. Staff Meet., Mayo Clin. **10**:726 (Nov. 13) 1935.

testicular tissue was replaced completely by fibrous connective tissue. In the other, the tubules were largely fibrosed and replaced with hyalin. In the testes of 4 of the 5 patients in the seventh decade of life, the tubules showed fibrosis and hyalinization of varying degrees. From this study it seems that the 13 testes from patients in the first four decades of life and at least 1 from a patient in the fifth decade might have been able to produce a mature germinal epithelium if the organs had been placed in the scrotum, and that atrophy and degeneration of the testicular tubules progress with age in the undescended testis.

MacCarty [55] said that tumor of intra-abdominal undescended testes is rare. Only a few cases have been noted at the Mayo Clinic, and a small number have been presented in the literature. Undescended testes are rather common. Tumor of descended testes occurs comparatively frequently. In view of these facts MacCarty has been conservative in advice as to the procedure in an uncomplicated case of intra-abdominal testis. It should not be removed simply because of its position, although it might rarely become malignant. The inguinal testis is more liable to injury, and injury as a frequent stimulus to the production of a neoplasm in any place in the body can never be ignored.

Cabot [56] said that the conclusions as to the possibility of regeneration of the tubular portions of the testis following its placement in a normal position are based almost entirely on animal experimentation. These experiments suggest that extensive degeneration of the tubular epithelium may take place and yet be followed by a practically complete restoration to normal if the testis is again placed in a normal position. Such observations are significant not only in the management of undescended testis in a child but also in the advising of the adult patient. Pace's studies appear to show that degeneration and hyalinization of the tubules are slowly progressive; he further suggests that at least in his series the degeneration and hyalinization are not complete until the fifth decade of life or even later. From this it appears that replacement of the undescended testis should be advised for the adult patient at least up to his fortieth year. The observations also discourage the habit of performing orchidectomy on rather incomplete evidence.

SPERMATIC CORD

Division.—Burdick and Higinbotham [57] have practiced complete division of all the structures comprising the spermatic cord as an aid in the cure of certain types of inguinal hernia. In some cases it was

55. MacCarty, W. C., in discussion on Pace,[54] p. 728.

56. Cabot, Hugh, in discussion on Pace,[54] p. 729.

57. Burdick, C. G., and Higinbotham, N. L.: Division of the Spermatic Cord as an Aid in Operating on Selected Types of Inguinal Hernia, Ann. Surg. **102**:863 (Nov.) 1935.

observed at operation that the vessels had been practically destroyed without necrosis of the testis. The spermatic cord was intentionally divided, and it was found that the testis did not slough. The indications for this radical procedure are: recurrence of hernia in a patient more than 50 years of age in whom there have been one or more unsuccessful attempts at a radical cure and in whom the opposite testis is apparently normal; recurrence of hernia in a younger man who is incapacitated for his usual occupation and who has an apparently normal testis on the opposite side; large scrotal hernia in an aged person which is either irreducible or cannot be satisfactorily retained by a truss, and large sliding hernia.

In order to obtain the maximal benefit in saving time, the spermatic cord must be divided early in the operation. A ligature is placed about the cord at the point where it emerges from the internal abdominal ring, and a second one is placed at the point where it enters the scrotum; the intervening tissue is excised. There is always considerable swelling, accompanied by redness of the skin and edema of the scrotum. In some of their cases, gangrene seemed imminent and in 4 of these cases it occurred. The patient is kept in bed for the usual time, depending on the type of hernia, and is advised to wear a suspensory until the swelling has entirely subsided.

Complete division of the spermatic cord had been used in the repair of inguinal hernia in 200 patients. The cord was divided on one side in 166 of the patients, and in 17 the hernia was repaired and the cord was divided on both sides. Nine patients died; 6 (3.2 per cent), in consequence of the operation; 1, of pneumonia three and a half years after operation; 1, of a fractured skull following an accident sixteen months after operation, and 1, of heart disease two years after operation. Of the wounds, 159 healed by primary union, 6 were drained at the lower angle at the time of operation and healed in from ten to thirty days, while 33 (17.5 per cent) became infected.

Of 169 patients on whom there were follow-up records, the condition of the testis was noted in only 79. A common observation was moderate swelling of the testis for one or two months after operation, followed by diminution in the swelling and return to normal; atrophy of the testis occurred in some of these patients. In one the testis remained swollen for six months, and in another, for a year. The testis was recorded as normal in size in 42 patients; 25 of these patients were followed for from one to five years. All patients who were subjected to bilateral division of the spermatic cord were found to have testes of normal size. Of the remaining patients, 11 had slight atrophy of the testis, and 11 others had atrophy to a half or less of the normal size. Of the 169 patients who returned for one or more examinations,

20 had recurrence of hernia; in 1 patient the hernia recurred as early as one month after operation, and in another, as late as thirty-nine months; the average interval between operation and recurrence was nine and five-tenths months.

Torsion.—Kinney [58] reported a case of torsion of the spermatic cord. About 250 cases of torsion of the spermatic cord have been reported in the literature. In many instances, atrophy of the testis unquestionably is the result of previous torsion of the cord. Early diagnosis is imperative, and in the majority of cases detorsion can be satisfactorily accomplished only if the patient is seen within an hour or so after torsion has occurred. Even if detorsion can be performed, atrophy of the testis usually occurs. Torsion of the cord can occur at any age but it occurs most frequently in adolescence. The etiology is of little significance in the prevention, diagnosis and treatment of this condition. The right spermatic cord and testis are involved in the ratio of about 3:2. The Prehn sign seems to be of definite value in the differential diagnosis of epididymitis and torsion of the spermatic cord. The treatment should be surgical, and an appeal is made for prophylactic treatment and for the inspection of the opposite side in all cases of torsion of the spermatic cord.

SCROTUM

Congenital Canals and Cysts.—Neff [59] reported 5 cases of congenital canals or cysts of the genitoperineal raphe and 1 case of a periurethral cyst. These canals and cysts are said to arise from epithelial rests incident to imperfect ventral fusion in the formation of the external genitalia or from masses of epithelial cells which have migrated from the primitive epithelium. The cysts and canals are therefore congenital. They have an epidermoid or mucous lining, depending on their cells of origin. The lining of the canals is almost invariably epidermoid; a smaller majority of the cysts show this type of lining. The canals of the raphe apparently manifest themselves only after infection, usually after gonorrheal infection. The canals may become infected without involvement of the urethra. The treatment of both canals and cysts is surgical.

URINE

Diversion of Urinary Stream.—Cabot and Scherer [60] said that exstrophy of the bladder is the most outstanding of the congenital

58. Kinney, W. H.: Torsion of the Spermatic Cord, J. Urol. **34**:470 (Nov.) 1935.

59. Neff, J. H.: Congenital Canals and Cysts of the Genito-Perineal Raphe, Tr. Am. A. Genito-Urin. Surgeons **28**:415 (June) 1935.

60. Cabot, Hugh, and Scherer, R. G.: Choice of Methods of Diverting the Urinary Stream Above the Level of the Bladder, Ann. Surg. **102**:849 (Nov.) 1935.

anomalies for which diversion of the urinary stream above the level of the bladder may be necessary. Closely allied to this condition is the severe grade of epispadias, which may be defined as a situation in which the superior wall of the urethra is missing together with the sphincteric mechanism of the neck of the bladder. A third type of anomaly suitable for this procedure is an undefined condition in which there apparently is some congenital defect in the nerve mechanism controlling the musculature of the urinary tract. Diversion of the urinary stream may be indicated for certain injuries of the bladder or ureters. This statement includes the unusually large vesicovaginal fistula, often in cases in which several attempts at operative cure have failed. When the stage is reached at which there is insufficient tissue with which to construct a satisfactory floor of the bladder, diversion of the urine above that level must be considered. Injury of one or both ureters occasionally occurs in pelvic operations, most commonly in operations for cancer. Inflammatory (nontuberculous) cystitis is another condition for which this procedure is suitable. Cabot and Scherer were of the opinion that, although the latter condition may be described by a variety of names, it really is an extensive chronic interstitial cystitis. Another suitable condition is tuberculous cystitis, usually secondary to renal tuberculosis. At the outset the diagnosis of unilateral surgical tuberculosis may have been satisfactorily made and nephrectomy done. Sometimes, the tuberculous cystitis never subsides sufficiently to allow reasonable comfort. In this group of cases of cystitis resulting from tuberculosis and in the preceding one of cases of nontuberculous origin drainage of the bladder by suprapubic cystostomy fails to give satisfactory relief. It is further significant that when nephrectomy has been performed for tuberculosis, the ureter of the remaining kidney is frequently abnormal and often reveals considerable dilation, apparently the result of an increased thickness of the wall of the bladder caused by hypertrophy produced by frequency of urination. For this condition cystostomy will not be satisfactory. Finally, there is the relatively large group of cases of cancer of the bladder in which the growth encroaches or will encroach on one or both ureters and in which the satisfactory removal or destruction of the tumor will fail to relieve the patient. For those of these lesions in which resection of the wall of the bladder is considered advisable, reimplantation of the ureter offers a satisfactory solution.

There are three methods of diverting the urinary stream: nephrostomy, uretero-enterostomy and cutaneous ureterostomy. Since nephrostomy, except for temporary diversion of the urine, is preferred to pyelostomy, the latter method is not discussed. Nephrostomy diverts the urine at the level of the kidney. Its advantage over other methods is that it does not involve the division of the ureter. It may, therefore,

be employed as an intermediate stage, when, owing to conditions, such as the proximity of a recent serious abdominal operation, no rearrangement of the ureter can properly be undertaken. Entero-anastomosis has gained in favor since the technic suggested by Coffey, that is, oblique introduction of the ureter into the bowel, began to be generally used. This operation is technically difficult and requires familiarity with the surgery of the urinary, as well as of the intestinal, tract. The outstanding danger is that of infection either in connection with the operation or at various subsequent periods, owing to an ascending ureteritis and pyelonephritis which have previously been subject to periodic exacerbations. Cutaneous ureterostomy was first undertaken many years ago. Like uretero-enterostomy, it involves complete separation of the ureter from the bladder, and to this extent is permanent. It is technically a simple operation as compared with uretero-enterostomy, and the drainage is good if properly managed. The danger of infection is probably no more than that involved in intestinal anastomosis, and should a severe infection occur, the ureter is accessible for irrigation and drainage. It is particularly applicable to the abnormal ureter, which is more readily managed by this technic than is the normal one.

Nephrostomy is perhaps at its best as a temporary expedient until a more permanent arrangement, such as reimplantation of the ureter into the bladder, possibly uretero-ureteral anastomosis or ureterointestinal anastomosis, may be performed. The patients most favorable for uretero-enterostomy are children who have exstrophy or epispadias and whose ureters are normal. The operative mortality for these patients, provided the appropriate technic is used, should be less than 5 per cent. The next most suitable group will be patients whose bladders are seriously involved but whose ureters have remained normal. Cutaneous ureterostomy is the method of election for the majority of patients whose ureters are grossly abnormal. This is particularly the choice for patients with vesical tuberculosis of an intolerable and intractable type, whether the condition is bilateral inoperable tuberculosis of the kidney, tuberculosis of a remaining kidney after nephrectomy or an intractable lesion of the bladder with the condition of the remaining kidney normal except for some dilation and atony of the ureter. For these patients relief may be expected. The duration of life will depend on the condition of the kidneys as concerns infection with tuberculosis.

Essential Hematuria.—Colella [61] concluded, after an intensive study of 10 cases of hematuria and an exhaustive review of the literature,

61. Colella, P. R.: Sul meccanismo di azione della decapsulazione e risultati prossimi e remoti della stessa nella cura della nefrite emorragica, Arch. ital. di urol. **12**:695 (July) 1935.

that in evaluating the results of decapsulation of the kidney a clearcut distinction must be made between the cases of essential hematuria, which he calls "hemorrhagic nephritis," and cases of hematuria in which the condition must be regarded as the expression of a definitely inflammatory condition (nephropyelitis or pyelonephritis with hemorrhagic manifestations). While it is true that this conception of "essential hematuria" as an entity is accepted only with reluctance by the majority of urologists, the need of differentiating between this condition and hematuria in which the bleeding is clearly inflammatory in origin has recently been discussed by Heitz-Boyer and others in the Société Francais d'Urologie in terms that it is impossible to ignore. Although from the point of view of pathogenesis and symptomatology the inflammatory forms of renal hemorrhage and the forms of simple hematuric nephritis are scarcely distinguishable, owing to the difficulty of determining the cause of the hematuria, this distinction must definitely be made with reference to the form of treatment to be employed in order not to discredit the true value of decapsulation when applied with discrimination in suitable cases.

Colella reported 10 cases in which he carried out decapsulation. In 9 of these the results were just what he had hoped for, and the hematuria came promptly to an end. In the tenth case decapsulation had no effect because the patient was suffering from acute and chronic lesions of pyelonephritis accompanied by hemorrhagic manifestations; in this case, nephrectomy was necessary to stop the bleeding.

Colella concluded that decapsulation acts on the supply of intrarenal blood by a mechanism that is chiefly nervous and of a vasodilating nature. Hence it follows that this procedure is justifiable only in cases in which an increase of pressure, caused by vasoconstriction, may set up a sudden disequilibrium of the circulation with consequent obstruction of the free outflow of blood—a disequilibrium which, as it increases through the persistence of nervous stimuli, not well defined and perhaps toxic, paves the way for hemorrhagic phenomena as time goes on. The general conception is that the decapsulated kidney permits the passage of a greater amount of blood in a given time or that it has a better blood supply than does the nondecapsulated one. Since the number of afferent vessels is unchanged, it follows that the increased supply of blood is referable to an increased velocity of circulation within the kidney or to a greater fulness of its vascular bed; in other words, to vasodilatation, with diminution of intramural circulatory resistance, especially within the capillaries. This is the argument for the value of the procedure in essential hematuria.

In conditions that are clearly inflammatory (pyelonephritis) hyperemia is already present, in the conception of inflammation, and if

to this there is superadded a special exalted toxic and pathogenic power of the bacteria and their toxins hematuria may be the result not only of a more rapid and sudden vasodilator congestion but also of lesions of the walls of the vessels. Histologic observations bear out this assertion and explain why decapsulation in such a case gives results that are either transitory or entirely negative, as in Colella's tenth case. In cases of essential hematuria, however, he is of the opinion that decapsulation is the method of choice to stop the hemorrhage, for he believes that it gives lasting results in a high percentage of the cases.

Pyuria.—Hepler [62] said that within recent years there has been a growing recognition of the importance of a complete urologic examination of the infant when there is presumptive evidence of disease of the urinary tract. This increasing application of modern diagnostic methods to urologic conditions in children has established a number of facts, the most significant of which are that congenital narrowing of the caliber of the urinary tract, chiefly at the points of normal anatomic narrowing, is common, and that congenital obstruction is an important factor in urinary diseases both in children and in adults; chronic infections are usually secondary to or are perpetuated by these obstructions, and chronic or recurrent pyuria almost invariably indicates some anatomic defect; further, disease of the urinary tract among children is often obscured by symptoms pointing to other conditions, frequently gastro-intestinal disorders.

Infants and children do not localize their subjective symptoms, and many of the lesions do not produce symptoms. Pyuria is the most significant sign of urogenital disease in children.

From a study of 694 infants and children during a period of nine months at the Children's Orthopedic Hospital, Seattle, it was concluded that catheterization is necessary in the diagnosis of urinary disease in children. Ninety-nine per cent of 692 patients had pus in the voided urine, and only 13 per cent had pus in the catheterized specimen. The amount of pus in urine which is properly collected is no indication either of the kind or of the severity of the disease of the urinary tract. In the 24 patients in whom there was demonstrable disease of the urinary tract exactly similar lesions existed, and the number of pus cells in the urine varied from less than 1 to more than 20 per high-power dry field. Fifty per cent of the children who had demonstrable disease of the urinary tract, including a number who had advanced lesions and severe infections, had fewer pus cells in the urine than the number which is frequently established as normal. If a persistent or recurrent pyuria, regardless of the number of pus cells, is taken as a criterion for a com-

62. Hepler, A. B., and Scott, R. T.: The Significance of Pyuria in Children, J. A. M. A. **105**:499 (Aug. 17) 1935.

plete renal study, a number of children will be subjected to what is apparently an unnecessary examination, for only 37 per cent of the 64 who had pus cells in the catheterized specimen had demonstrable disease of the urinary tract. Only 9 of the 26 children in the study who had disease of the urinary tract had subjective symptoms that were referable to the urinary tract. Urinary complications in children who have tuberculosis of the bones and joints are not common, and prolonged immobilization on frames or in casts does not tend to produce urinary stasis, infection or formation of stones. Forty-one of the children examined had tuberculosis of bones or joints. Tubercle bacilli were not found in the urine after repeated and careful examinations. Only 7 had pus in the urine, and none of these had any demonstrable disease of the urinary tract.